“COMPARING RADIOTHERAPY WITH 4 GY x 5 FRACTIONS VS 3 GY x 10 FRACTIONS FOR METASTATIC SPINAL CORD COMPRESSION”

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DEPARTMENT OF RADIOTHERAPY
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CHENNAI – 600 003

CERTIFICATE

This is to certify that the dissertation entitled **"COMPARING RADIOTHERAPY WITH 4GY x 5 FRACTIONS VS 3GY x 10 FRACTIONS FOR METASTATIC SPINAL CORD COMPRESSION"** submitted by Dr.HARISH KUMAR.PR, in partial fulfillment for the award of the degree of Doctor of Medicine in Radiotherapy by the Tamil Nadu Dr.MG.R. Medical University, Chennai is a bonafide record of the work done by him in the Department of Radiotherapy, Madras Medical College during the academic year 2016-2019.

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CERTIFICATE OF THE GUIDE

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Place :
Date :

DECLARATION

I, Dr. HARISH KUMAR.PR. solemnly declare that the dissertation titled **"COMPARING RADIOTHERAPY WITH 4 GY x 5 FRACTIONS VS 3 GY x 10 FRACTIONS FOR METASTATIC SPINAL CORD COMPRESSION"** has been prepared by me and submitted to Tamil Nadu Dr. MGR Medical university, Chennai in partial fulfilment of the rules and regulations for the M.D degree examination in radiotherapy.

Date: **DR. HARISH KUMAR.PR**

Place:

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CONTENTS

Introduction

INTRODUCTION

Compression of spinal cord by metastatic tumour is an emergency scenario in oncology. If not treated appropriately it can lead to serious neurological compromise. It commonly occurs due to extension of vertebral metastases into the epidural sac[1].

Metastatic spinal cord compression (MSCC) is the compression of the dural sac and its contents by extradural mass. Neurological impairment occurring due to compression of the spinal cord if not treated early will become irreversible leading to permanent neurological deficit[2].

EPIDEMIOLOGY

MSCC occurs in 10% to 15% of patients having cancer. Autopsy series have demonstrated that around 5% patients dying of cancer have cord compression at autopsy[3].

Median interval from the diagnosis of cancer clinically to the development of cord compression is approximately 6 months to 1 year. Late development of vertebral metastases and consequently MSCC is seen in breast cancer[4].

Common primaries causing MSCC in adults include breast, prostate, lung, lymphoma, and myeloma[5]. Melanoma, renal cell carcinoma, sarcoma, thyroid carcinoma are also associated with MSCC. In paediatric population cord compression has been associated with neuroblastoma, sarcoma and lymphoma[6].

MSCC can also occur in the absence of a known primary tumour. 20% MSCC present in this fashion. Cord compression as a presenting manifestation occurs in Non-Hodgkin's lymphoma, myeloma, and small cell lung carcinoma.

>75% MSCC occur in thoracic spine, 20-30% in lumbar spine, 10-20% in cervical spine. These values are roughly in proportion to the volume of vertebral bodies in each region.

It is found that certain tumours have a predilection to certain spinal regions where they spread and cause MSCC. Lung and Breast primaries spread more frequently to thoracic spine; Genitourinary and Gastrointestinal primaries have a predilection for lumbar spine.

Multiple non-contiguous metastases and cord compressions occur in 10-30% patients. Tumour location in multiple non-contiguous presentations is found commonly in the anterior or anterolateral spinal canal. Around 10% patients develop a recurrent cord compression in a different untreated level within 6 months of the first event[7].

ANATOMY OF SPINAL CORD

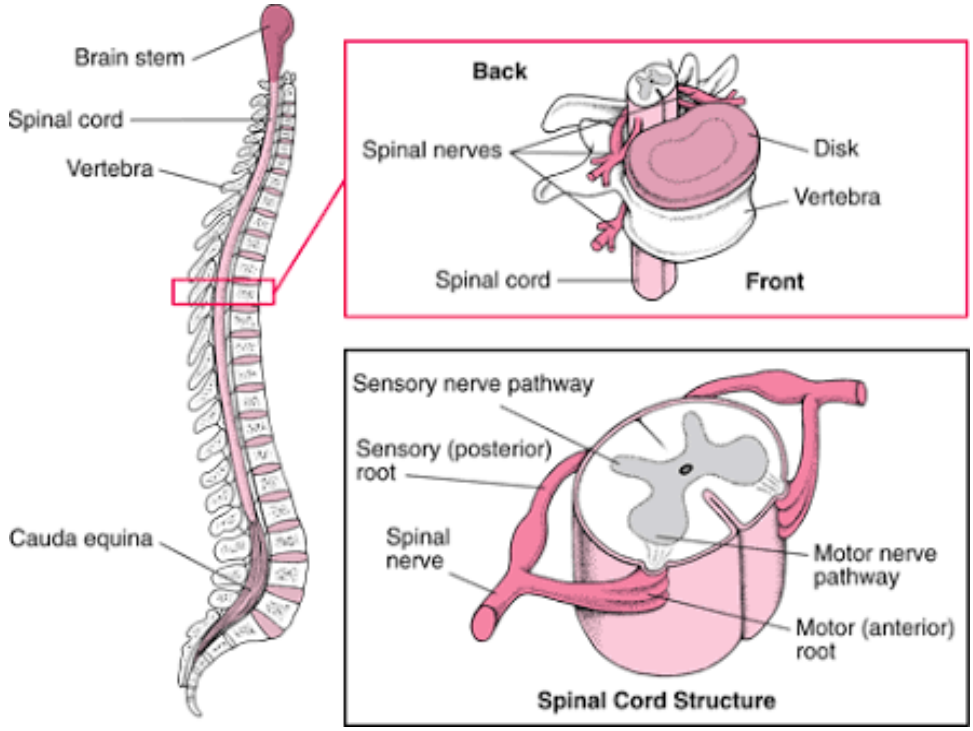

FIGURE 1 – SPINAL CORD GROSS ANATOMY

Posterior boy surface and neural arch of each vertebrae form the vertebral foramina. Vertebral foramina in continuity form the spinal canal. Spinal cord continues down from medulla oblongata and runs through the spinal canal.

The foramina of cervical and thoracic vertebra are triangular and the cord is mobile in these regions. Foramina of thoracic vertebra are rounded and hence the spinal canal is more rigid. Notches from the pedicles of continuous vertebra form the intervertebral foramen through which the spinal nerves pass.

Spinal cord is cylindrical in shape and composed of functional segments in correspondence to 31 pairs of spinal nerves – eight cervical, twelve thoracic, five lumbar, five sacral and five coccygeal.

The spinal cord like brain is covered by meninges composed of dura mater, arachnoid mater, and pia mater.

The outer dura mater is a fibrous barrier between spinal cord and spinal canal. Dural sac ends at the level of S2-3 whereas the dura continues till the coccyx along with filum terminale.

The middle arachnoid mater lying between dura and pia consists of the subarachnoid space through which CSF flows. Arachnoid mater and subarachnoid space continue till dural sac.

The inner pia mater covers the spinal cord and its vasculature. It condenses to form the dentate ligaments suspending the cord to dura.

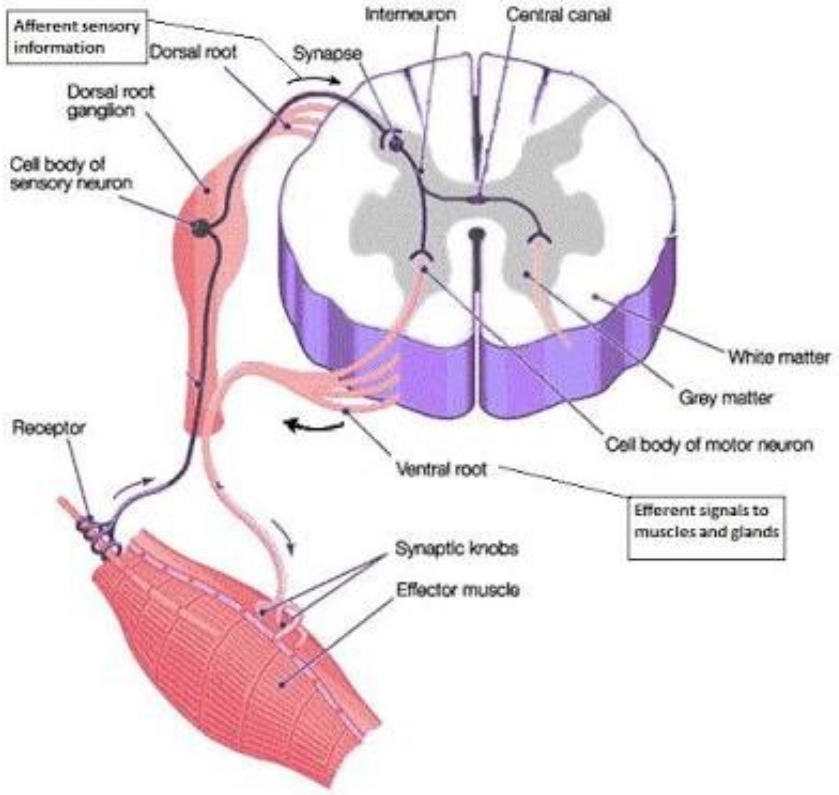

FIGURE 2- CROSS SECTION OF SPINAL CORD

Spinal cord consists of inner gray matter and peripheral white matter. Gray matter consists of neuronal bodies and white matter consists of axons.

Anterior horns of gray mater control motor functions, lateral horns control autonomic functions, posterior horns control sensory functions.

Anterior and lateral white matter axonal tracts including corticospinal tracts control fine motor and tone. Lateral spinal thalamic tract is associated with pain perception.

Spinocerebellar tract is involved in transmission of muscle tone and stretch sensations. Positional and fine touch sensations are transmitted by dorsal column tracts.

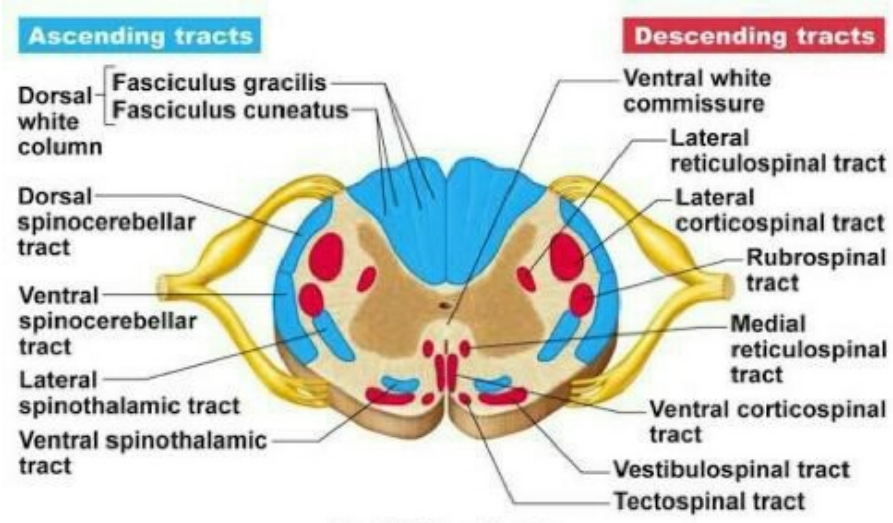

FIGURE 3 - SPINAL CORD TRACTS

The vertebral column grows faster than spinal cord during childhood and hence spinal cord is shorter than vertebral column and ends around L1 vertebral body in adults. Below L1 thecal sac consists of the lumbar, sacral and coccygeal nerves which form the cauda equina.

PATHOPHYSIOLOGY

20-30% of patients having cancer develop spinal vertebral metastases. Epidural and vertebral venous plexus (Batson's plexus) are low pressure valve less circulation systems which drain the intra-abdominal and intrathoracic organs.

Their flow and frequent reversal of flow seen in them depend on the intra-abdominal and intrathoracic pressures. They form a suitable transport system for cancer cells to spine.

Secretion of bone derived growth factors, and cytokines facilitate the deposition and growth of metastases.

Cord compression due to metastatic tumour can occur by one of the following mechanisms:

- The vertebral bone metastasis can grow and continue into the spinal cord.
- A paravertebral mass can pass through the neural foramina i.e., trans foraminal progression and compress the cord. This type of spread has been observed with neuroblastoma and lymphomas.
- The metastatic deposit can grow and destroy the vertebra leading to collapse or displacement of bony fragments which may impinge on the cord and cause compression.
- Certain tumour deposits can involve the posterior spinal elements and impinge the nerve roots. This occurs only rarely though.

- A very rare possibility is the direct spread of metastatic deposit to spinal cord causing compression. Intramedullary metastasis has been reported rarely in literature.
- Aggressive paravertebral primary tumours like pancoast tumour can invade the anatomical barriers, erode the bone and directly cause compression of cord.

The pathological effects of compression of spinal cord are not fully understood. Consequent development and establishment of neurological impairment has been studied extensively[8,9].

Histopathologic examinations reveal demyelination and necrosis of white matter at the level of compression with relatively well preserved gray matter.

The following steps elucidate the progression of spinal cord injury leading to neurological disability

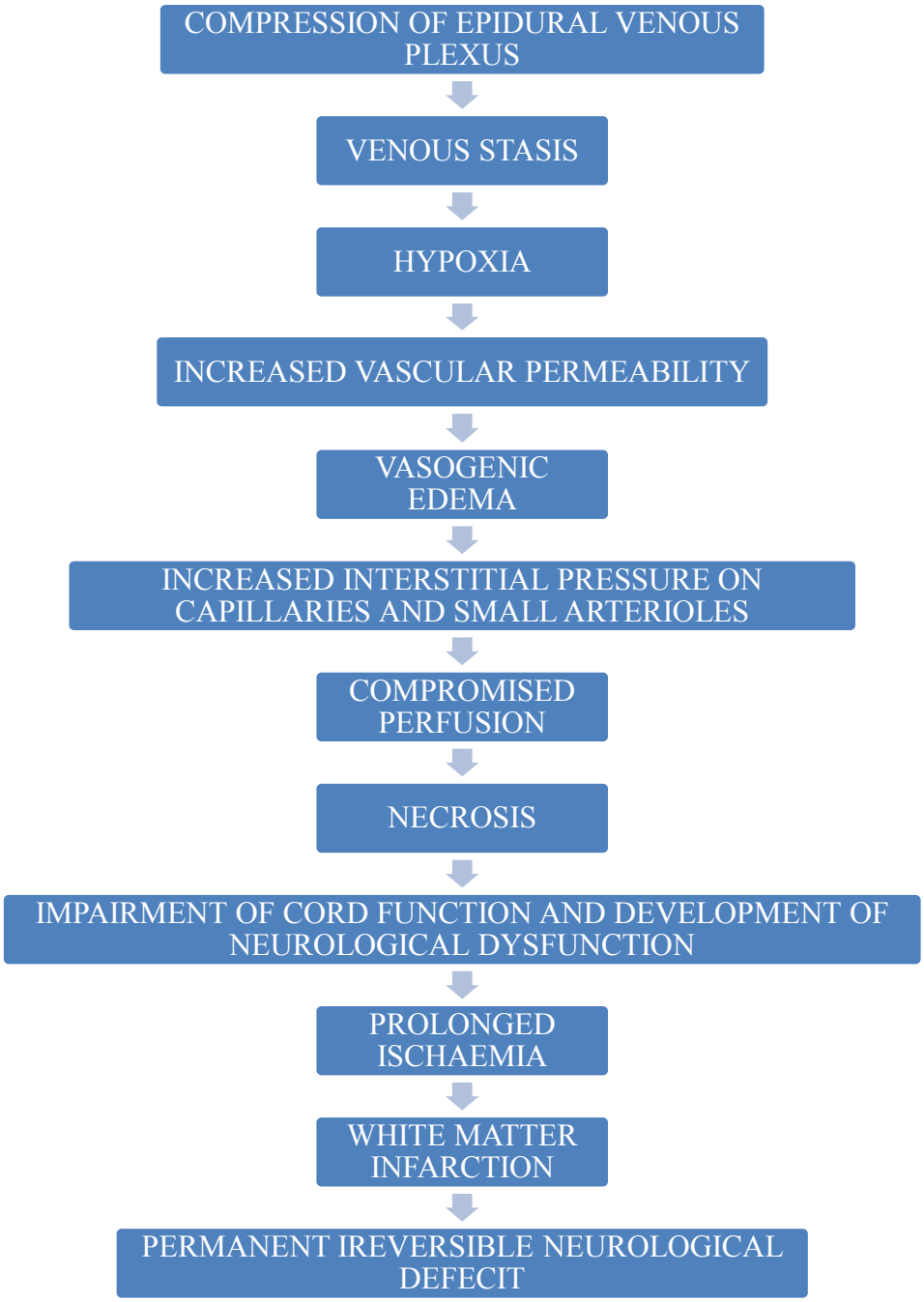

FIGURE 4- PATHOPHYSIOLOGY OF CORD COMPRESSION

CLINICAL PRESENTATION

Presenting symptoms of MSCC include pain, motor weakness, sensory deficit and autonomic dysfunction in decreasing order of frequency.

The most common presenting symptom in a patient with compression is pain. Pain is present in 90-95% of patients. Pain can be localized or radicular in nature. Pain is also the earliest symptom of MSCC. Pain precedes the diagnosis of MSCC by days to months in clinical practice.

A clinical dictum is that is that any back pain in a cancer known to spread to spine or epidural space must be taken as a metastatic pain until otherwise proven.

Localized back pain or cervical pain occurs due to destruction and expansion of the vertebral bone. Involvement of the richly innervated periosteum causes localized pain in early stages. A tender vertebra on percussion is a clinical feature at this stage.

Epidural mass effect causes severe pain which is exacerbated by coughing, sneezing, valsalva manoeuvre and recumbent position. Patients have a higher intensity of pain while awakening due to the effect of recumbence and as lesion progresses the may not be able to sleep because of pain.

Pain due to degenerative joint disorder must be excluded promptly. It occurs rarely outside the lower cervical and lower lumbar region and is reduced by recumbence. However in any back pain in a cancer patient the possibility of cord compression must be carefully evaluated.

Radicular pain is caused due to compression of nerve roots. Lumbar and cervical radiculopathies are unilateral while thoracic radiculopathies are bilateral. Lumbosacral radiculopathy is aggravated by straight leg raising and crossed straight leg raising manoeuvres.

Neurological symptoms which form the second most presenting feature of MSCC develop in days to weeks after the onset of pain and proceed to deficit in hours to days. Motor dysfunction occurs earlier followed by sensory and autonomic dysfunctions.

Thoracic spine being the commonest site of MSCC paraparesis is the first motor symptom in patients which progresses to paraplegia. Leg heaviness, difficulty in climbing stairs are the complaints given.

Cervical cord compression can lead to quadriparesis. Respiratory insufficiency is seen in higher cervical cord involvement. Upper lumbar cord compression causes lower limb weakness.

Paraplegic patients have a poor prognosis in spite of early intervention. Duration to develop deficit varies with primary also. Lung cancer has a rapid onset and progression of motor deficit than breast cancer. In any cancer patient with back pain, osteolysis, and bone scan positivity cord compression should be carefully evaluated and expected even in the absence of neurological deficit.

Sensory disturbance is less common than motor disturbance. Diminished sensation two to three levels below level of compression is noted. Conus medullaris syndrome causes saddle paraesthesia.

New onset nocturia, hesitancy and urinary retention point towards bladder dysfunction due to autonomic system involvement.

DIAGNOSIS OF MSCC

The average duration between onset of symptoms and the diagnosis has been around 3 months during which the neurologic deficit becomes irreversible.

High degree of clinical suspicion is necessary to diagnose cord compression at an early stage. Atypical back pain, change in the nature of pre-existing back pain, pain not responding to medications, pain aggravated in supine position and pain located in thoracic spine warrant an evaluation to rule out compression the spinal cord.

MRI is the standard imaging technique of choice[10]. Plain x-ray, high resolution CT, CT myelography, bone scintigraphy, PET scans have also been used but are inferior to MRI in diagnosing MSCC.

Plain x-ray lacks sensitivity and specificity. Only 80% of vertebral metastases at the level of cord compression can be made out with x-ray film. Multiple levels of involvement, presence of a paraspinal mass causing compression, transforaminal involvement cannot be made out with a plain x-ray film.

The imaging modality which was the preferred standard in the pre-MRI era was myelogram with or without CT. When there is contraindication to MRI computed tomography and myelogram are the preferred imaging modality.

MRI has high sensitivity (93%), high specificity (97%), and high accuracy (95%) in detecting spinal cord compression. MRI can delineate the anatomy of cord, soft tissues and bone non-invasively. Multiple levels of compression[10] can be found out in a single imaging. Metastasis capable of compressing the cord can be identified at its early stage[11,12] and can also be differentiated from other pathologic process by MRI[13,14].

Bone scintigraphy is a useful screening method to diagnose bone metastases but it lacks resolution, sensitivity, and specificity to diagnose cord compression by bone metastases. Moreover lytic lesions of myeloma will be undetected by bone scintigraphy. PET scan is also useful as a screening method but cannot provide the anatomic details necessary for diagnosis.

In patients who do not have a known history of cancer the diagnosis of metastatic cord compression needs either an image guided incisional biopsy[15] or an excisional biopsy of the mass to confirm the diagnosis.

A metastatic epidural mass can obliterate the subarachnoid space completely creating the possibility of herniation after the pressure is relieved at the level below obstruction. Although this is a rare possibility considering the seriousness of such a condition lumbar puncture must be avoided in a patient suspected to have MSCC.

PROGNOSTIC FACTORS FOR FUNCTIONAL OUTCOME

Motor deficit is the most important and devastating clinical outcome of MSCC with autonomic dysfunction and sensory dysfunction resulting in lesser proportion of patients.

Functional outcome which predominantly includes return of motor function depends on severity of neurological damage at initiation of treatment, rapidity of development of neurological deficit and histology of primary tumour.

The most important prognostic factor deciding outcome of treatment is the severity of neurological damage at the time of initiation of treatment.

Retrospective data show that 80-90% of patients treated earlier before the onset of neurological deficit remain ambulant. 50% of patients treated at an early stage with mild transverse myelitis and 1-5% of patients treated at a later stage when they develop paraplegia maintain or regain ambulance after treatment.

Multivariate analysis showed an improved functional outcome in pre therapy ambulant patients. These studies emphasize strongly on the early detection and treatment of metastatic cord compression to preserve ambulance.

Rapid development of neurological deficit predicts a poor functional outcome and also possible predicts irreversible spinal cord infarction. Slower development of motor deficit is associated with an improved functional outcome.

Multivariate analysis of a prospective study conducted by Rades et al[16] showed that the strongest predictor of ambulation post therapy was the time to develop motor deficit before radiation from the start of any symptoms. Ambulatory recovery was found in 86%, 55% and 35% of patients with a history of >14 days, 8-14 days and 1-7 days for development of motor deficit respectively.

Tumour histology was predictive of functional outcomes in multivariate analysis especially after treatment with radiation. Radiosensitive tumours have better functional outcome.

Late functional return from 6 months to 2 years has been documented in long term survivors of non-hodgkin lymphoma.

SURVIVAL IN MSCC

Survival in untreated patients is in the order of few months. Median survival in treated patients is 3-16 months[17]. Death occurs due to systemic progression of primary tumour.

Survival depends on the type of primary tumour. Median survival is 17-20 months for breast cancer, and prostate cancer compared to 4 months for lung cancer. Lymphoma and myeloma patients live longer than patients with solid tumours.

SCORING SYSTEMS

TABLE 1- TOKUSHI SCORING SYSTEM – REVISED

PREDICIITVE FACTORS	**SCORE**
GENERAL CONDITION (KPS)	
KPS 10%-40%	0
KPS 50%-70%	1
KPS 80%-100%	2
NUMBER OF EXTRASPINAL BONE METSTATIC FOCI	
>3	0
2	1
1	2
NUMBER OF METASTASES IN VERTEBRAL BODY	
>3	0
2	1
1	2
METASTASES TO MAJOR INTERNAL ORGANS	
UNREMOVABLE	0
REMOVABLE	1
NO METASTASES	2
PRIMARY SITE OF CANCER	
LUNG, STOMACH, OSTEOSARCOMA, BLADDER, ESOPHAGUS, PANCREAS	0
LIVER,GALL BLADDER, UNIDENTIFIED	1
OTHERS	2
KIDNEY, UTERUS	3
RECTUM	4
THYROD,PROSTATE,BREAST,CARCINOID	5
SPINAL CORD PALSY	
COMPLETE (FRANKEL A,B)	0
INCOMPELETE (FRANKEL C,D)	1
NONE (FRANKEL E)	2
TOTAL POINTS	**MEAN SURVIVAL**
0-8	< 6 MONTHS
9-11	> 6 MONTHS
12-15	> 12 MONTHS

TABLE 2- TOMITA SCORE

PROGNOSTIC FACTOR	**POINTS**
PRIMARY TUMOUR	
SLOW GROWTH (BREAST, THYROID)	1
MODERATE GROETH 9KIDNEY, UTERUS)	2
RAPID GROWTH (LUNG,STOMACH)	4
VISCERAL METASTASES	
TREATABLE	2
UNTREATABLE	4
BONE METASTASES	
SOLITARY OR ISOLATED	1
MULTIPLE	2
TOTAL POINTS	**PREDICTED PROGNOSIS**
2-4	> 2 YEAR
4-6	1-2 YEARS
6-8	6-12 MONTHS
8-10	< 3 MONTHS

TABLE 3- MODIFIED BAUR SCORE

PROGNOSTIC FACTORS	**POINTS**
NO VICERAL METASTASES	1
NO LUNG CANCER	1
PRIMARY TUMOUR= BREAST,KIDNEY,LYMPHOMA,MULTIPLR MYELOMA	1
ONE SOLITARY SKELETAL METASTASES	1
TOTAL POINTS	**MEDIAN SURVIVAL**
0-1	4.8 MONTHS
2	18.2 MONTHS
3-4	28.4 MONTHS

TABLE 4- LINDEN SCORE

PROGNOSTIC FACTORS	POINTS
KPS	
80-100	2
50-70	1
20-40	0
PRIMARY TUMOUR	
BREAST	3
PROSTATE	2
LUNG	1
OTHER	0
VISCERAL METASTASES	
NO	1
YES	0
TOTAL POINTS	**MEAN SURVIVAL**
0-2	4.8 MONTHS
4-5	13.1 MONTHS
6	18.3 MONTHS

TABLE-5 RADES SCORE

PROGNOSTIC FACTORS	SCORE
PRMARY TUMOUR	
BREAST	8
PROSTATE	7
MYELOMA/LYMPHOMA	5
LUNG	3
OTHERS	4
OTHER BONE METASTASES	
NO	8
YES	7
VISCERAL METASTASES	
YES	2
NO	8
INTERVAL FROM DIAGNOSIS TO MSCC	
< 15 MONTHS	4
> 15 MONTHS	7
AMBULATORY STATUS BEFORE RT	
AMBULATORY	7
NON AMBULATORY	3
TIME OF DEVELOPING MOTOR DEFICITS BEFOE RT	
1-7 DAYS	3
8-14 DAYS	6
> 14 DAYS	8
TOTAL SCORE	6 MONTH SURVIVAL %
20-30	16
31-35	48
36-46	81

TABLE 6- KATAGIRI SCORE

PROGNOSTIC FACTOR	SCORE
PRIMARY LESION	
RAPID GROWTH (LIVER, STOMACH, LUNG)	3
SLOW GROWTH (BREAST, PROSTATE,LYMPHOMA,THYROID,MYELOMA)	0
MODERATE GROWTH (OTHERS)	2
VISCERAL OR CEREBRAL METASTASES	2
ECOG 3 OR 4	1
PREVIOUS CHEMOTHERAPY	1
MULTIPLE SKELETAL METASTASES	1
TOTAL SCORE	6 AND 12 MONTHS SURVIVAL
0-2	97.9; 89.1
3-5	70.6; 48.8
6-8	31.3; 10.9

Review of Literature

LITERATURE REVIEW OF MANAGEMENT

CORTICOSTEROIDS

Corticosteroids should be started as soon as diagnosis of MSCC is suspected. The main effects of steroids in the setting of cord compression are

Reduction in back pain

Reduction in vasogenic oedema of cord

Prevent additional damage due to reduced perfusion and progression of neurological symptoms.

Sorensen et al[18] conducted a randomised control trial conducted in MSCC patients treated by radiation with or without the addition of corticosteroids. 96 mg IV bolus dexamethasone followed by 96 mg per day oral administration for 3 days followed by a 10 day taper was the schedule followed. 3 months and 6 months ambulatory rates of 81% vs 63% and 59% vs 33% (p-value <0.5) were reported in the study. Also 11% patients in treatment arm had >grade 3 toxicity.

Vecht et al[19] compared IV loading doses of 10 mg vs 100 mg followed by 16 mg per day oral regimen in both arms and found no significant difference in ambulatory rate, pain reduction and bladder function.

Heimdal et al[20] had compared 96 mg IV dexamethasone per day tapered in 2 weeks with 4mg IV dexamethasone per day tapered in 2 weeks. 14.3% serious gastrointestinal events where seen in high dose arm.

One fatal ulcer haemorrhage, one rectal bleeding and two bowel perforations were reported. The ambulatory rates between arms were not significant.

Compiling the data from these studies it is clear that steroids play an important role in MSCC and the benefit from moderate doses are comparable to high dose steroids with minimal toxicity.

10 g of IV dexamethasone loading followed by maintenance with 4-6 mg every 6-8 hours and tapered in 2 weeks is a sufficient regimen clinically. Proton pump inhibitors prophylaxis for gastrointestinal effect is recommended while steroids are started.

SURGERY

There are mixed results in literature comparing the benefit of surgical procedures in metastatic cord compression. Several factors can influence the outcome of surgery.

Patchell et al[21] conducted a randomised phase III trial comparing radiation alone (3 Gy x 10 #) versus decompression and stabilization surgery followed by same radiation dose within two weeks. This study was closed prematurely due to an interim analysis showing significantly better ambulatory rates in surgery arm.

This study established a statistically significant improvement in ambulatory rates, maintenance of continence; better scores predicting spinal cord function after injury; better median morphine and dexamethasone equivalent doses needed and improved median overall survival all favouring surgery.

However the results in radiation alone arm in this study was inferior to published data of irradiation alone in MSCC. Mechanical cause of compression which might need surgical intervention was not an exclusion criterion in this study. Hence any such patients might have been treated with RT alone leading to poorer results.

A secondary analysis of this study demonstrated that benefit of surgery decreases with increase in age and showed no benefit beyond 65 years of age[22].

A meta-analysis comparing surgery and radiation in treatment of MSCC showed that ambulatory rate was significantly higher in surgically treated patients and they were 1.3 times more likely to be ambulatory. The surgery data in this analysis was from uncontrolled cohort studies[23].

A retrospective analysis compared 122 patients treated with surgery followed by radiation with 244 patients treated only by radiation alone matched with 11 prognostic factors found that treatment method did not impact outcome and survival[24].

Young et al[25] randomised 29 patients to laminectomy followed radiation vs radiation and found no benefit to surgery in terms of pain relief, ambulation, or sphincter function.

Laminectomy does not remove the tumour bulk and it may actually worsen spinal stability in vertebral body collapse or in kyphosis. Tumour mass resection and stabilization of spine is the preferred procedure. Several single institution of small sample sizes have shown improved results over surgery with such surgical approaches.

Surgery has its own morbidity and its use depends on performance status and expected survival outcome. Surgery has a definitive role in stabilising the spine when fracture is present, and in progressive disease or recurrence following irradiation.

Surgery can establish the pathologic diagnosis in an unknown primary for which CT guided percutaneous biopsy is an alternate. In clinical practice only 15-20% patients become eligible for a primary surgical resection.

SCORING SYSTEM TO DECIDE BETWEEN SURGERY AND RADIATION

Decision of treatment modality in vertebral metastases is based largely on clinical judgement. Patients with good performance status and spinal instability are considered for surgical fixation.

Spinal instability neoplastic score (SINS) is a scoring system which has been developed to decide the role of surgical intervention. It has been prospectively validated. Studies have shown good inter-observer agreement in using the score.

TABLE 7- SPINAL INSTABILITY NEOPLASIA SCORE

FACTORS	**POINTS**
LOCATION	
JUNCTIONAL C1-C2,C7-T2,T11-L1,L5-S1	3
MOBILE C3-C6,L2-L4	2
SEMIRIGID T3-T10	1
RIGID S2-5	0

FACTORS	POINTS
PAIN	
MECHANICAL PAIN PAIN WITH MOVEMENT OR SPINAL LOADING, IMPROVES WITH RECUMBENCY	3
OCCASIONAL PAIN	1
PAINLESS	0
BONE LESION	
LYTIC	2
MIXED	1
BLASTIC	0
SPINAL ALIGNMENT	
SUBLUXATION/TRANSLATION	4
DE NOVO KYPHOSIS/SCOLIOSIS	2
NORMAL ALIGNMENT	0
VERTEBRAL BODY COLLAPSE	
> 50% COLLAPSE	3
<50% COLLAPSE	2
NO COLLAPSE WITH > 50% VERTEBRAL BODY INVOLVEMENT	1
NONE	0
POSTERIOR SPINAL ALIGNMENT	
BILATERAL	3
UNILATERAL	1
NONE	0
TOTAL SCORE	**INFERENCE**
0-6	STABLE
7-12	POTENTIALLY UNSTABLE
13-18	UNSTABLE

RADIATION THERAPY

Multiple radiation fractionation schedules have been used in the management of MSCC. 30 Gy delivered in 10 fractions is a common palliative regimen followed.

Considering the heterogeneity in characteristics and survival outcomes in MSCC depending on primary tumour a single radiation fractionation cannot be considered as standard for all subset of patients.

Maranzano et al[26] in a randomised control trial compared a short course regimen of 16 Gy in 2 fractions of 8 Gy given in a 6 day gap with a longer course regimen of 5 Gy in 3 fractions followed by 3 Gy in 5 fractions after a gap of 4 days reaching a total dose of 30 Gy.

This study reported a similar outcome in pain relief (56% vs 59%), maintenance of ambulation (68% vs 71%) and preservation of bladder function (90% vs 89%). This study concluded by recommending 8Gy x 2 fractions regimen for treatment of MSCC.

This study had assessed two hypo fractionated regimens which are not practiced as a standard. The outcome when defined as regaining of motor and sphincter function was significantly lower. 29% had regained motor function and 14% had regained sphincter function. Another notable point is that 5% patients progressed to paraplegia without in-field recurrence and this might have been due to radiation induced spinal toxicity due to the large fraction size.

Maranzano et a27 in a subsequent randomised trial compared single 8 Gy radiation versus 16 Gy delivered in two 8 Gy fractions 6 days apart in patients expected to have poor survival.

They found equivalent results when assessing the median duration of response and overall survival and concluded that single 8 Gy radiation can be used effectively for the palliation of MSCC with minimal toxicity and patient inconvenience.

Both these studies did not compare the regimens with the more commonly followed 30 Gy in 10 fractions regimen.

Rades et al[28] retrospectively reviewed 1304 patients treated by different fractionated regimes for MSCC such a : 8 Gy x 1 fraction; 4Gy x 5 fractions; 3 Gy x 10 fractions; 2.5 Gy x 15 fractions; 2 Gy x 20 fractions.

Post treatment ambulatory rates were similar in all groups ranging from 63 % to 74% and motor function improvement ranged from 26% to 31%. Though this study did not show any difference in ambulatory outcomes it did show a significant difference in 2 year in field recurrence rates. The recurrence rates from shorter to longer regimen were 24%, 26%,14%,9%,7%.

Rades et al[29] published a randomised control trial in 2016 comparing 30 Gy in 10 fractions and 20 Gy in 5 fractions for treatment of MSCC in patients with expected poor to intermediate survival. 226 patients were randomised to both arms and were evaluated for motor outcomes.

The ambulatory rate and progression free survival were not statistically significant between the two arms. They concluded that short course radiation was not significantly inferior to longer course in MSCC patients with intermediate to poor survival.

TABLE 8- RADIATION THERAPY FRACTIONATION TRIALS IN MSCC

Author	Number of patients	Short course regime	Long course regime	Ambulation rates
NON RANDOMISED TRIALS				
Rades 2004[30]	214	30Gy in 10#	40Gy in 20#	68% vs 71%
Rades 2005	1304	8Gy in 1# 20Gy in 5#	30Gy in 10# 37.7Gy in 15# 40Gy in 20#	68.5% vs 67%
Rades 2011	231	8Gy in 1# 20Gy in 5#	30Gy in 10# 37.7Gy in 15# 40Gy in 20#	84% vs 84%
RANDOMISED TRIALS				
Maranzano et al 2005	300	16 Gy in 2#	15 Gy in 3# + 15 Gy in 5#	68%vs71%
Maranzano et al 2009	327	8 Gy in 1#	16 Gy in 2#	62% vs 69%
Rades et al 2016	233	20 Gy in 5#	30 Gy in 10#	74% vs 78.1%

None of the published data from randomised trials and nonrandomised series have shown an improvement in ambulatory rates with a particular radiation fractionation[31,32,33].

However in patients who are expected to have a longer survival of more than two years in field recurrences can play a significant role in causing morbidity to patient. Most patients presenting with MSCC have a poor survival and short course radiation might be well enough to provide palliation and maintain ambulance.

In patients expected to have longer survival due to the lack of concrete supportive data for short course regimen a longer course of radiation fractionation can be employed.

Aims and Objectives

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

To compare the overall response regarding motor function defined as improvement or no further progression at the end of 1 month in patients treated with two different fractionation schedules of 4 Gy x 5 fractions versus 3 Gy x 10 fractions for metastatic spinal cord compression

SECONDARY OBJECTIVE:

1) To compare the acute toxicities in the two arms

2) To assess the overall response at 6 months of treatment.

Material and Methods

MATERIALS AND METHODS

STUDY CENTRE:

Department of Radiotherapy, Barnard Institute of Radiology and Oncology, Rajiv Gandhi Government general hospital, Madras medical college.

STUDY DURATION

One year

STUDY DESIGN

Double arm prospective study

STUDY POPULATION

Patients with known biopsy proven tumour presenting with metastatic spinal cord compression causing lower limb motor dysfunction.

SAMPLE SIZE

30 patients in each arm

The study was reviewed and approved by the Institutional Ethical Committee.

INCLUSION CRITERIA

- ✓ Biopsy proven malignancy of any primary site
- ✓ Lower extremity motor dysfunction
- ✓ Radiological evidence of spinal cord compression

- ✓ Age-20 to 70 years
- ✓ No previous surgery to index site
- ✓ No previous irradiation to index site
- ✓ Patients with intermediate or poor survival prognosis

EXCLUSION CRITERIA

- ❖ No radiological evidence of bone metastasis
- ❖ Age <20 or >70 years
- ❖ Previous irradiation of the same spine
- ❖ Previous surgery of the same spine
- ❖ Metastasis of the cervical spine only
- ❖ Brain metastasis
- ❖ Primary Brain Tumour
- ❖ Major neurological disorders
- ❖ Established pathological fracture
- ❖ Spinal instability warranting surgical intervention

PRETREATMENT REQUIRMENTS

- ▪ Biopsy from primary tumour
- ▪ CT or MRI –spine

- Complete blood count, blood grouping
- Liver function test
- Renal function test
- Chest X ray – PA view
- ECG, Cardiology evaluation
- Ortho spine surgery consultation
- Medical records from previous consultations

TREATMENT PROTOCOL

Patients with a biopsy proven primary tumour diagnosed to have metastatic spinal cord compression causing lower limb dysfunction were identified. Imaging and clinical examination were correlated with deficit. Ortho spine surgeon consultation was done to rule out surgery. After getting consent patients were assigned to treatment arms by simple randomisation.

Patients in both arms received Inj. Dexamethasone 16 mg IV before start of radiation and were tapered over the period of treatment. All patients with vertebral metastases were given Inj. Zolendronate 4 mg every 28 days as per institution protocol followed.

Treatment volume included one vertebra above and below the involved vertebrae. Lateral margins encompassed the transverse process on either side. Treatment fields were defined and verified using x-ray simulation.

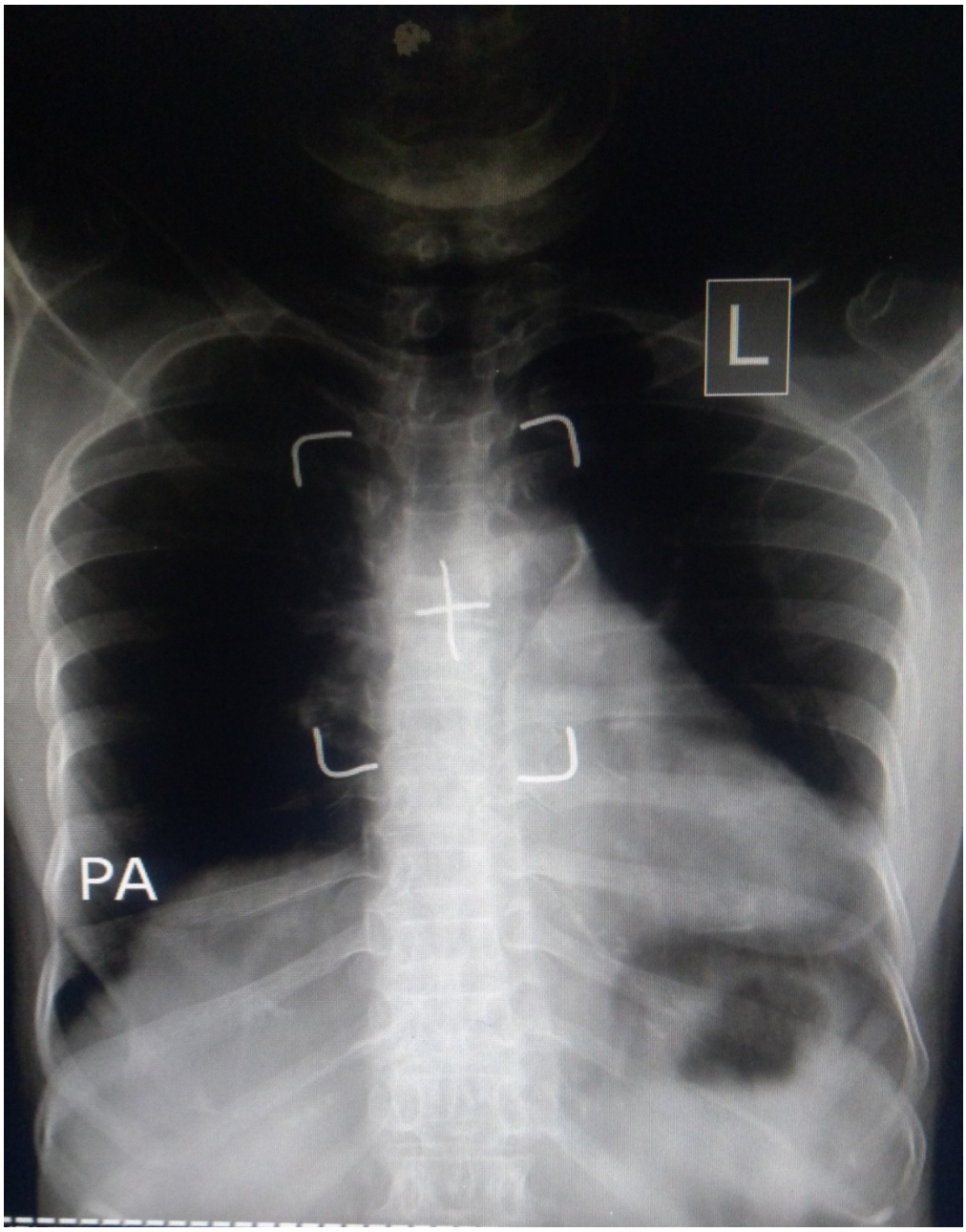

FIGURE 4- SIMULATION X-RAY

Radiation was delivered using Theratron phoenix telecobalt unit with single PA portal directly or by gantry rotation.

TABLE 9- PROTOCOL DESIGN

PROTOCOL	ARM A	ARM B
DOSE PER FRACTION	4 Gy	3 Gy
NUMBER OF FRACTIONS	5	10
TOTAL DOSE	20 Gy	30 Gy
DURATION OF TREATMENT	1 week	2 weeks

RADIOBIOLOGICAL COMPARISON

Biological effective dose is the product of total dose and relative effectiveness.

Relative effectiveness of a regimen is the relative effectiveness per unit dose for that fractionated treatment.

$$RE = 1 + d(\alpha/\beta)$$

d – Dose per fraction

α – Cell kill by linear component

β – Cell kill by quadratic component

Value of α/β:

Early reacting tissue (Tumour): 10

Late reacting tissue (Spinal cord): 3

$$BED = n\ d\ x\ [1+d(\alpha/\beta)]$$

Biologically equivalent dose is the equivalent dose in 2-Gy fraction i.e, total dose in 2-Gy fractions that would give the same log kill as the given schedule

$$EQD2 = BED\ /\ 1+[2\ /(\alpha/\beta)]$$

TABLE 10- RADIOBIOLOGICAL COMPARISON

	α/β	ARM A 4Gy x 5 #	ARM B 3Gy x 10#
TUMOUR			
BED	10	28 Gy_{10}	39 Gy_{10}
EQD2	10	23.3 Gy	32.5 Gy
CORD			
BED	3	46.67 Gy_3	60 Gy_3
EQD2	3	28 Gy	36 Gy

RESPONSE ASSESMENT

Clinical examination of lower limb motor function was done at baseline before radiation and 1, 3 and 6 months following radiation. It was scored as follows

0 – Total paralysis

1 – Palpable or visible contractions

3 – Active movement, full range of motion, against gravity

4 – Active movement, full range of motion, against gravity and provides some resistance.

5 – Active movement, full range of motion, against gravity and provides normal resistance.

Improvement of motor function was defined by improvement of point in scoring system compared to baseline.

Deterioration of motor function defined by reduction of point in scoring system compared to baseline

No further progression defined by no change in score compared to baseline

Primary end point was 1-month overall response regarding motor function defined as improvement or no further progression of motor deficits.

Secondary end point was local progression-free survival at 3 and 6 months

TOXICITY ASSESSMENT

Acute toxicity was assessed using RTOG scale

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Esophagus	Mild dysphagia/odynophagia may require soft diet and nonnarcotic analgesic	Moderate dysphagia/odynophagia may require liquid diet and narcotic analgesic	Severe dysphagia/odynophagia with dehydration, weight loss needing iv fluid or NG tube	Complete obstruction, ulceration,perfortion
Upper GI	Anorexia with <5% weight loss /nausea not requiring antiemetic/analgesic	Anorexia with <5% weight loss /nausea requiring antiemetic/analgesic	Anorexia with <15% weight loss /nausea not requiring iv fluid/NG tube	Ileus, obstruction, perforation, bleeding
WBC count	3000-4000	2000-3000	1000-2000	<1000
Platelet count	75000-100000	50000-75000	25000-50000	<25000 or spontaneous bleeding
Haemoglobin	11% - 9.5%	7.5% – 9.5%	5% - 7.5%	-
ANC	1500-2000	1000-1500	500-1000	<500 or sepsis

TABLE 11- RTOG TOXICITY GRADING

STATISTICAL ANALYSIS

Data was entered in Microsoft excel and SPSS software with Mann-Whitney U test was used for statistical analaysis

Analysis and Results

ANALYSIS AND RESULTS

PATIENT CHARACTRISTICS

TOTAL NUMBER OF PATIENTS

60 Patients were allocated to both arms by simple randomisation

ARM	NUMBER OF PATIENTS
A – 4 Gy x 5 fractions	30
B – 3 Gy x 10 fractions	30

TABLE 12- TOTAL PATIENTS

AGE DISTRIBUTION

AGE DISTRIBURION IN ENTIRE COHORT

AGE GROUP	NUMBER	PERCENTAGE
< 50	17	31.66%
50 – 60	30	50%
> 60	13	18.33%
TOTAL	60	100%

TABLE 13- AGE DISTRIBUTION IN COHORT

50% of patients in the protocol were between 50 and 60 years of age. 31.3% patients had age less than 50 years and 18.3% had age more than 60 years.

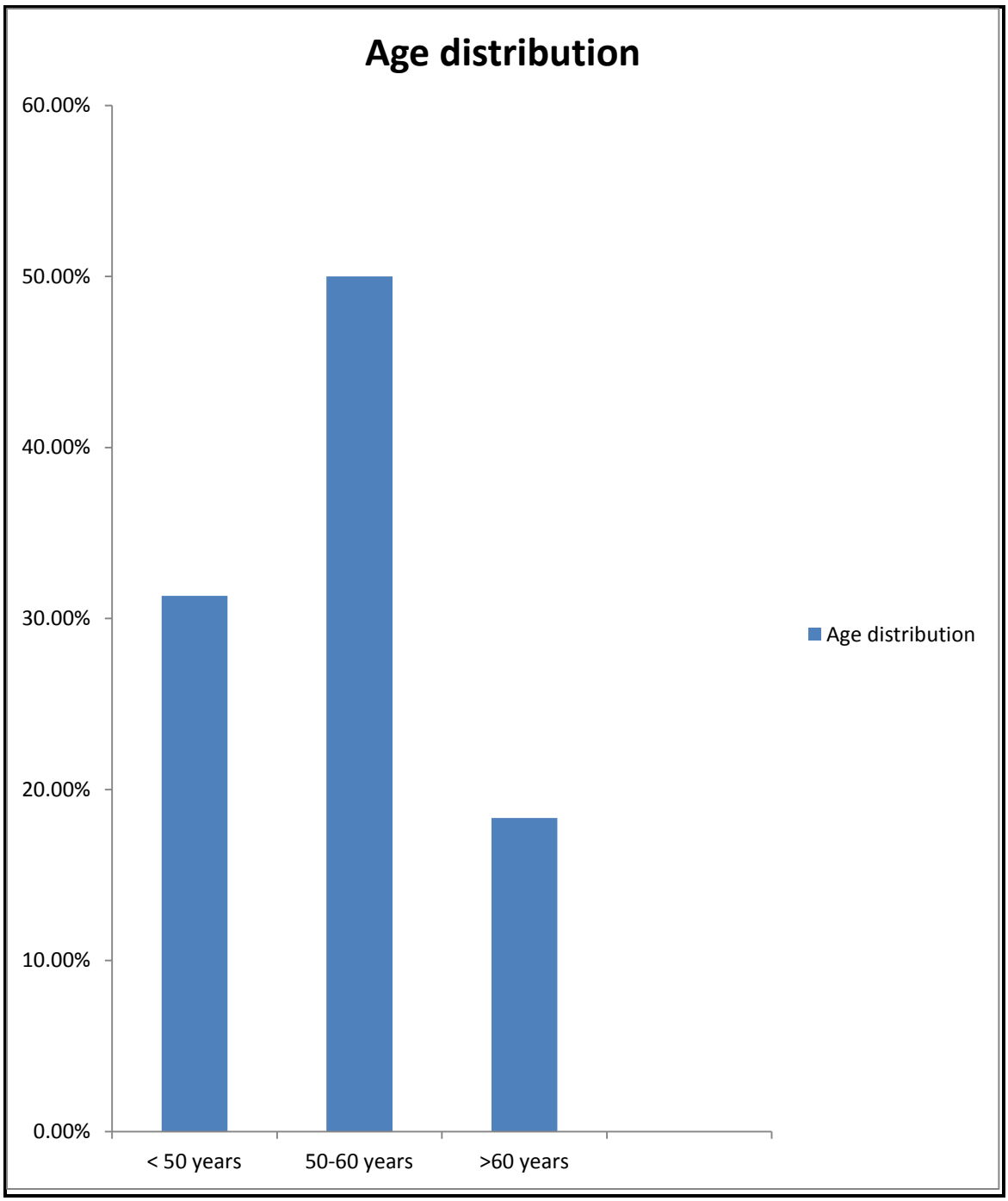

CHART 1- AGE DISTRIBUTION IN STUDY

AGE DISTRIBUTION IN EACH ARM

AGE GROUP	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
< 50	8	26.66%	9	30%	.64
50 – 60	14	46.66%	16	53.33%	
> 60	8	26.66%	5	16.66%	
TOTAL	30	100%	30	100%	

TABLE 14- AGE DISTRIBUTION

Arm A had 26.66% patients below 50 years, 46.66% patients between 50 and 60 years, 26.66% patients above 60 years. Youngest patient in Arm A was 40 years old and oldest patient was 72 years old. Arm B had 30% patients below 50 years, 53.33% patients between 50-60 years and 16.66% patients above 60 years. The youngest patient in Arm B was 37 years old and oldest patient was 68 years old.

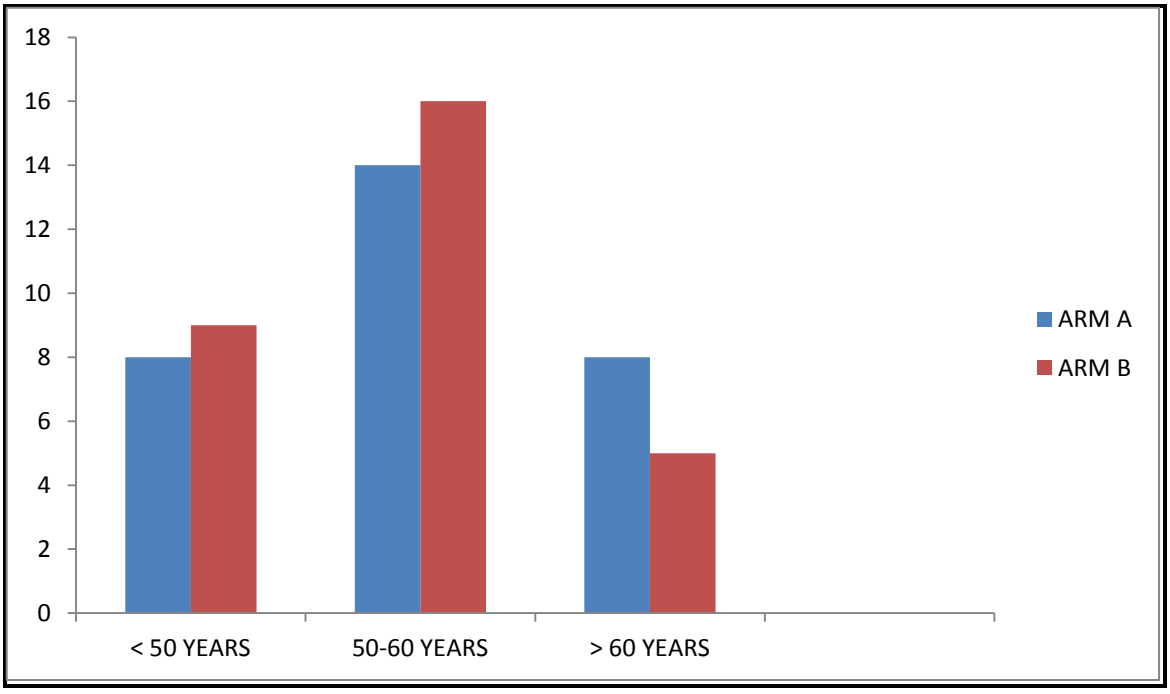

CHART 2- AGE DISTRIBUTION

GENDER DISTRIBUTION

GENDER	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
FEMALE	13	43.33%	12	40%	.79
MALE	17	56.66%	18	60%	
TOTAL	30	100%	30	100%	

TABLE 15- GENDER DISTRIBUTION

43.33% patients in ARM A were females and 56.66% were males.

40% patients in ARM B were females and 60% were males.

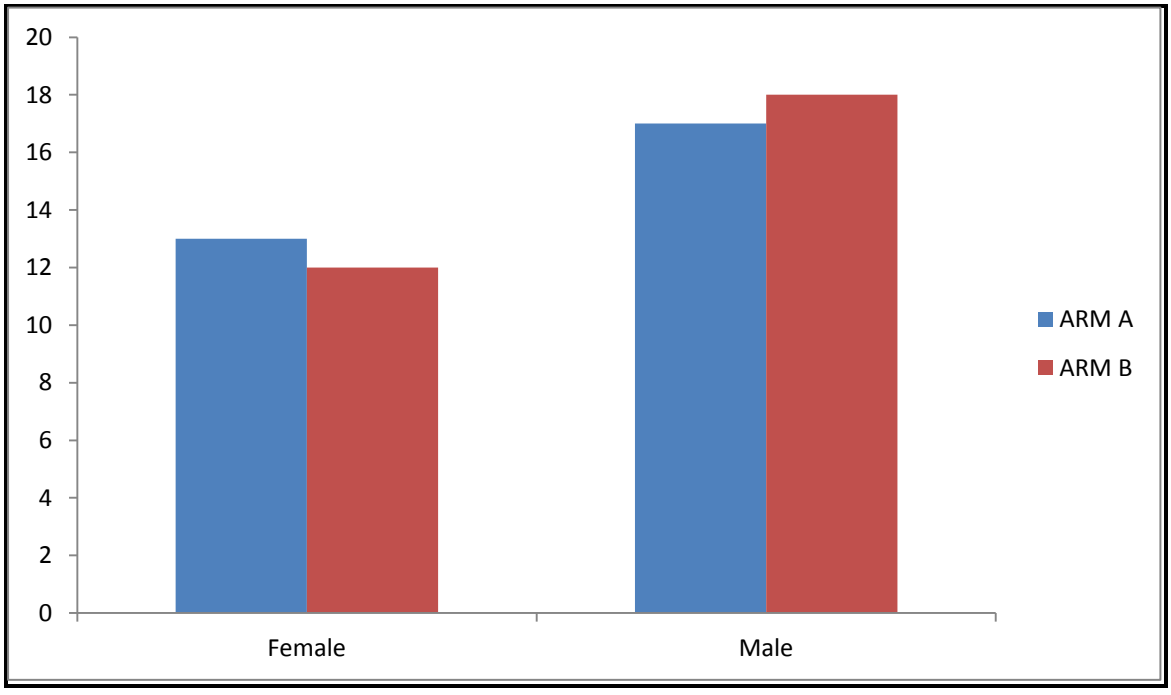

CHART 3- GENDER DISTIBUTION

PERFORMANCE STATUS

ECOG STATUS	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
1-2	5	16.66%	6	20%	.73
3-4	25	83.33%	24	80%	
TOTAL	30	100%	30	100%	

TABLE 16- PERFORMANCE STATUS

More than 80% patients in both arms had poor performance status of 3-4.

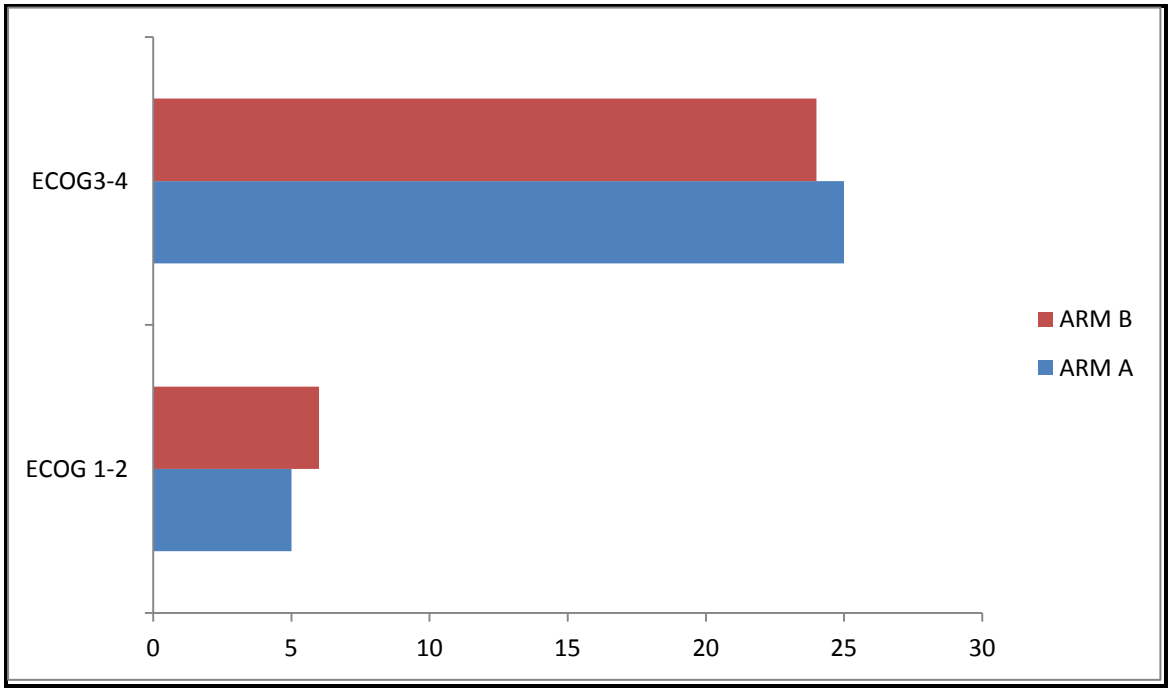

CHART 4- PERFORMANCE STATUS

NUMBER OF VERTEBRA INVOLVED

VERTEBRAL INVOLVEMENT	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
SINGLE	13	43.33%	12	40%	.79
MULTIPLE	17	56.66%	18	60%	
TOTAL	30	100%	30	100%	

TABLE 17- VERTEBRAL INVOLVEMENT

43.3% in ARM A had single vertebral involvement. 56.6% had multiple vertebral involvements. 40% in ARM A had single vertebral involvement.60% had multiple vertebral involvements.

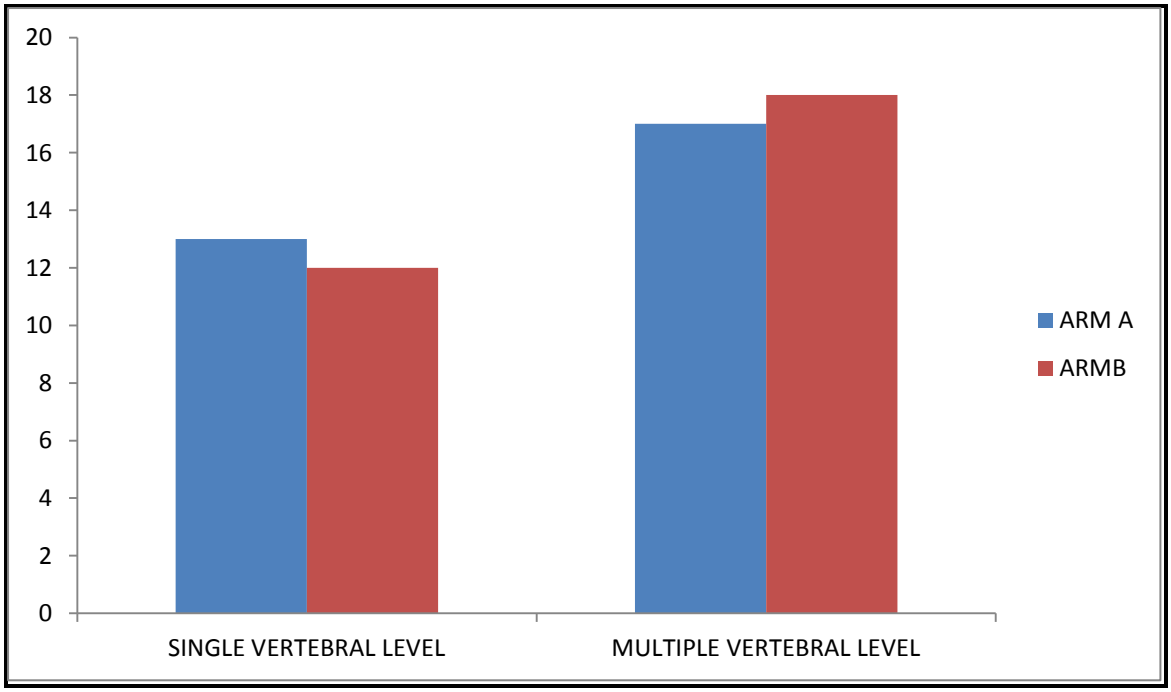

CHART 5- VETREBRAL INVOLVEMENT

PRESENCE OTHER BONE METASTASES

OTHER BONE METASTASES	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
YES	21	70%	20	66.66%	.78
NO	9	30%	10	33.3%	
TOTAL	30	100%	30	100%	

TABLE 18- OTHER BONE METASTASIS

70 % patients in ARM A had multiple bone metastases.

66.66% patients in ARM B had multiple bone metastases.

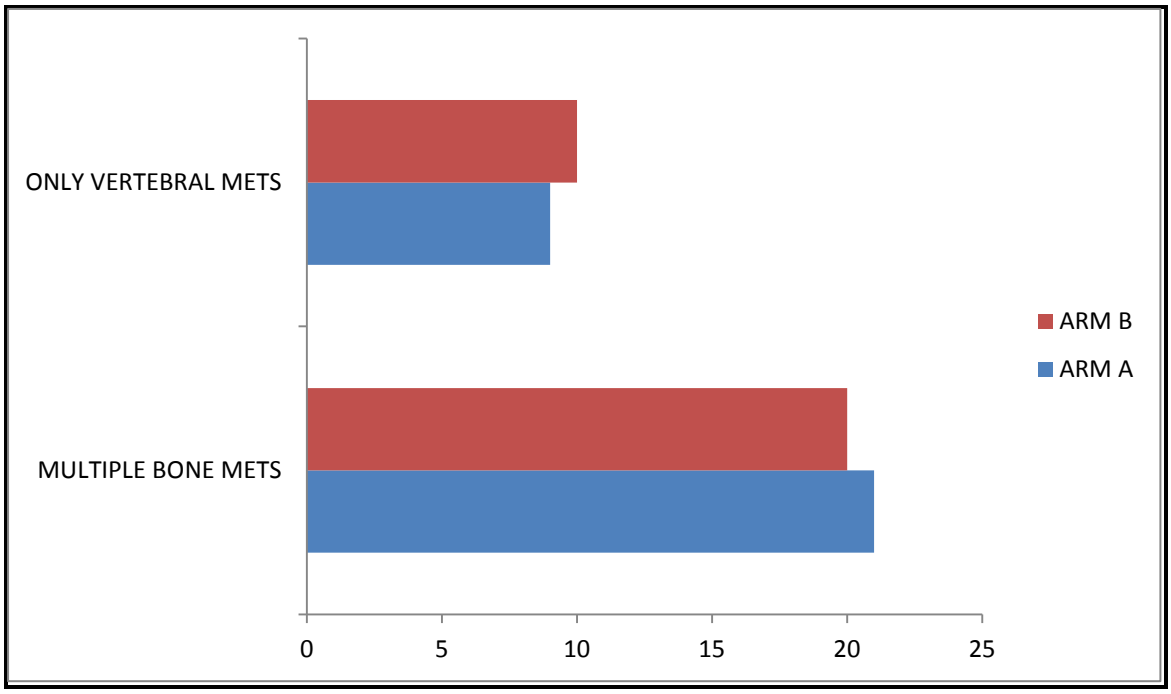

CHART 6- OTHER BONE METASTASIS

PRESENCE OF VISCERAL METASTASES

VISCERAL METASTASES	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
YES	22	73.33%	21	70%	.77
NO	8	26.66%	9	30%	
TOTAL	30	100%	30	100%	

TABLE 19- VISCERAL METASTASIS

More than 70% patients had visceral metastases in both arms

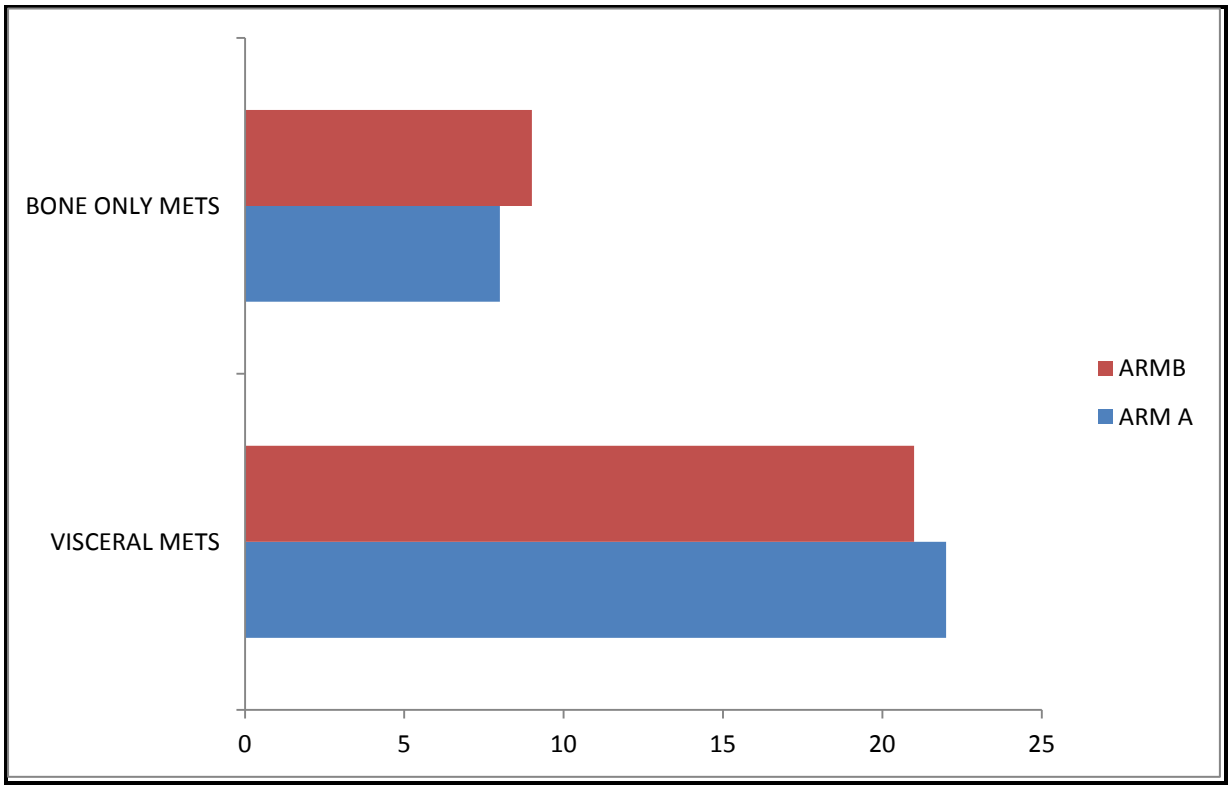

CHART 7- VISCERAL METASTASES

INTERVAL BETWEEN TUMUR DIAGNOSIS AND MSCC

INTERVAL	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
< 6 MONTHS	12	40%	10	33.33%	.59
> 6 MONTHS	18	60%	20	66.66%	
TOTAL	30	100%	30	100%	

TABLE 20- INTERVAL BETWEEN TUMUR DIAGNOSIS AND MSCC

40% patients in ARM A and 33.33% in ARM B developed MSCC within 6 months from tumour diagnosis.

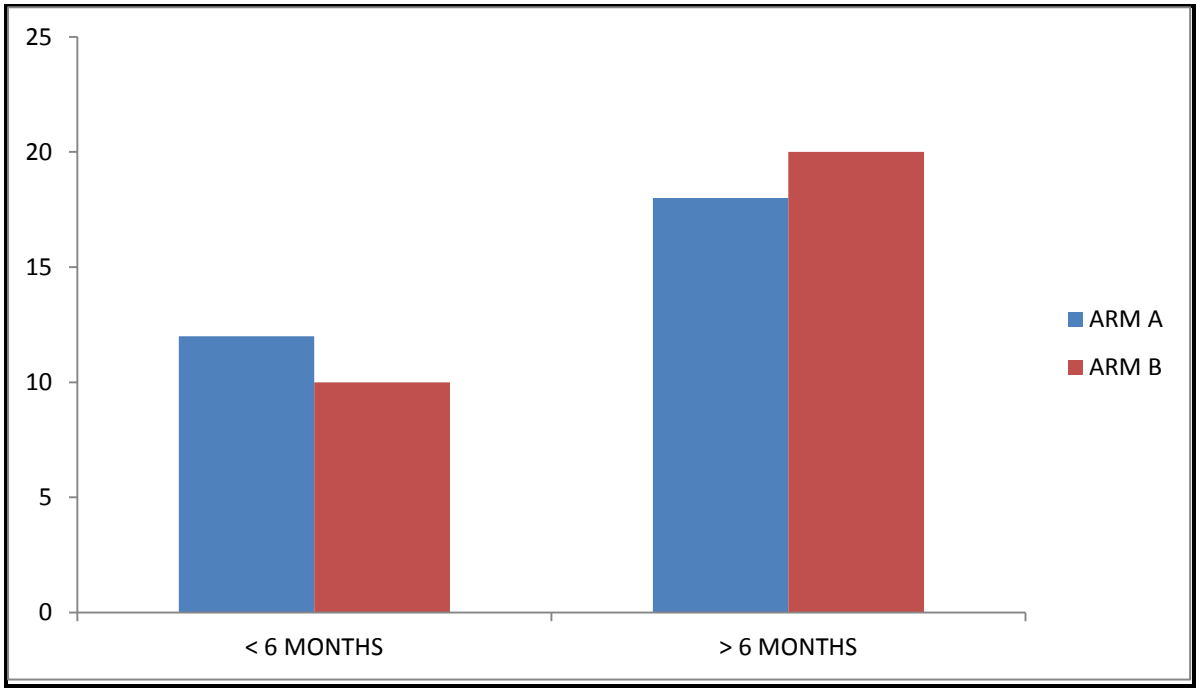

CHART 8- INTERVAL BETWEEN TUMUR DIAGNOSIS AND MSCC

PRIMARY SITE

PRIMARY SITE	ARM A		ARM B	
	NUMBER	PERCENT	NUMBER	PERCENT
LUNG	10	33.33%	7	23.33%
BREAST	7	23.33%	8	26.66%
PROSTATE	5	16.66%	6	20%
RECTUM	3	10%	4	13.33%
EOPHAGUS	3	10%	2	6.66%
STOMACH	0	-	1	3.33%
PANCREAS	1	33.33%	0	-
RCC	1	33.33%	1	33.33%
THYROID	0	-	1	33.33%
TOTAL	30	100%	30	100%

TABLE 21- PRIMARY SITE

Lung and breast primaries formed the majority of cases in both arms. 33.33% in AMR A and 23.33% in ARM B had lung primary. 23.33% in ARM A and 26.66% in ARM B had breast primary. Prostate was the next common primary constituting 16.66% patients in ARM A and 20% in ARM B. Other primaries found in study population were rectum, oesophagus, stomach, pancreas, thyroid, and renal cell carcinoma.

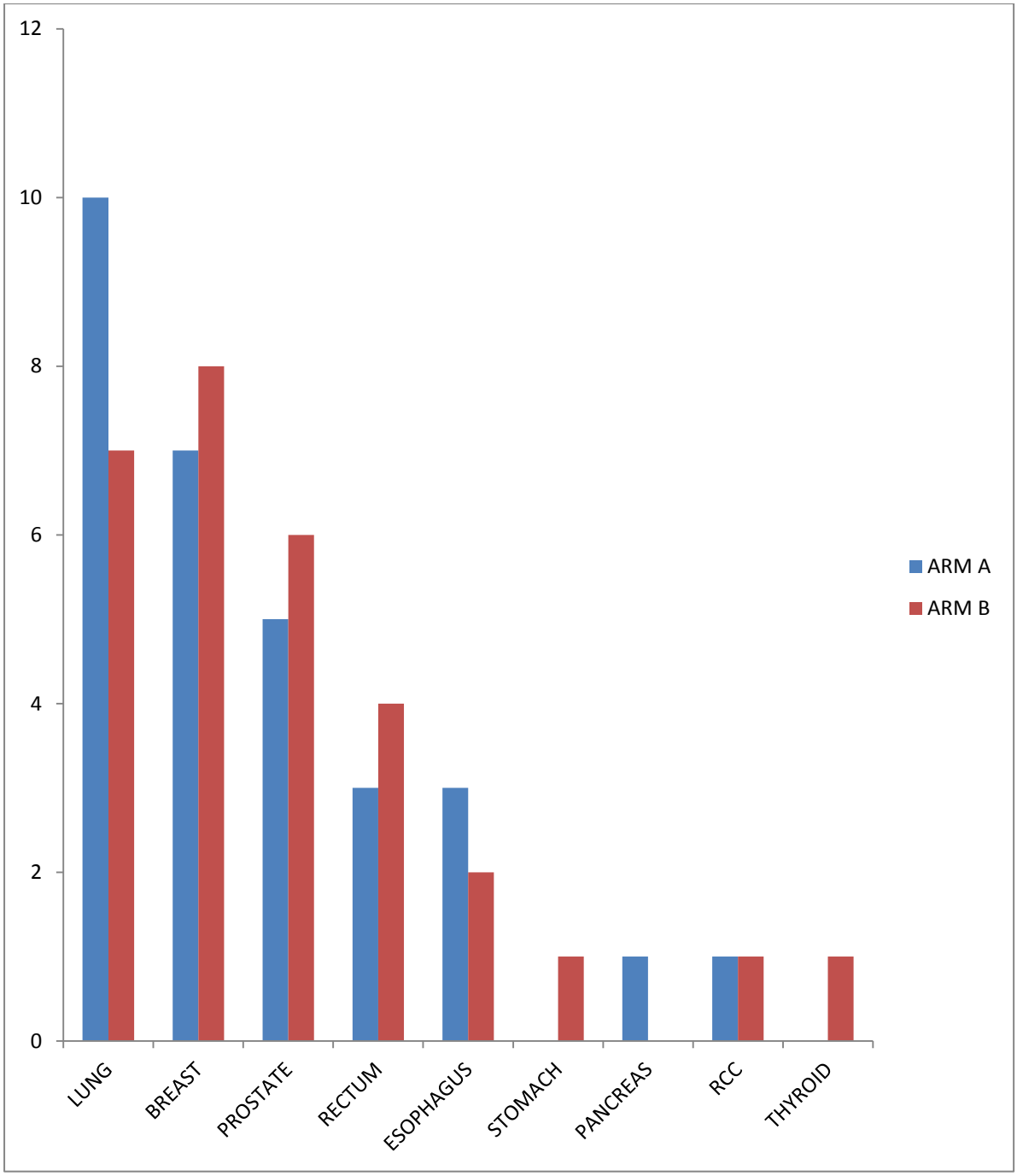

CHART 9- PRIMARY SITE

AMBULATORY STATUS BEFORE RADIATION

AMBULATORY STATUS	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
AMBULATORY WITHOUT AID	7	23.33%	8	26.66%	.94
AMBULATORY WITH AID	10	33.33%	11	36.66%	
NON AMBULATORY	13	43.33%	11	36.66%	
TOTAL	30	100%	30	100%	

TABLE 22- AMBULATORY STATUS BEFORE RADIATION

23.33% in ARM A and 26.66% in ARM B were ambulant without any aid.

33.33% in ARM A and 36.66% in ARM B were ambulant with aid.

43.33% in ARM A and 36.66% in ARM B were non ambulant.

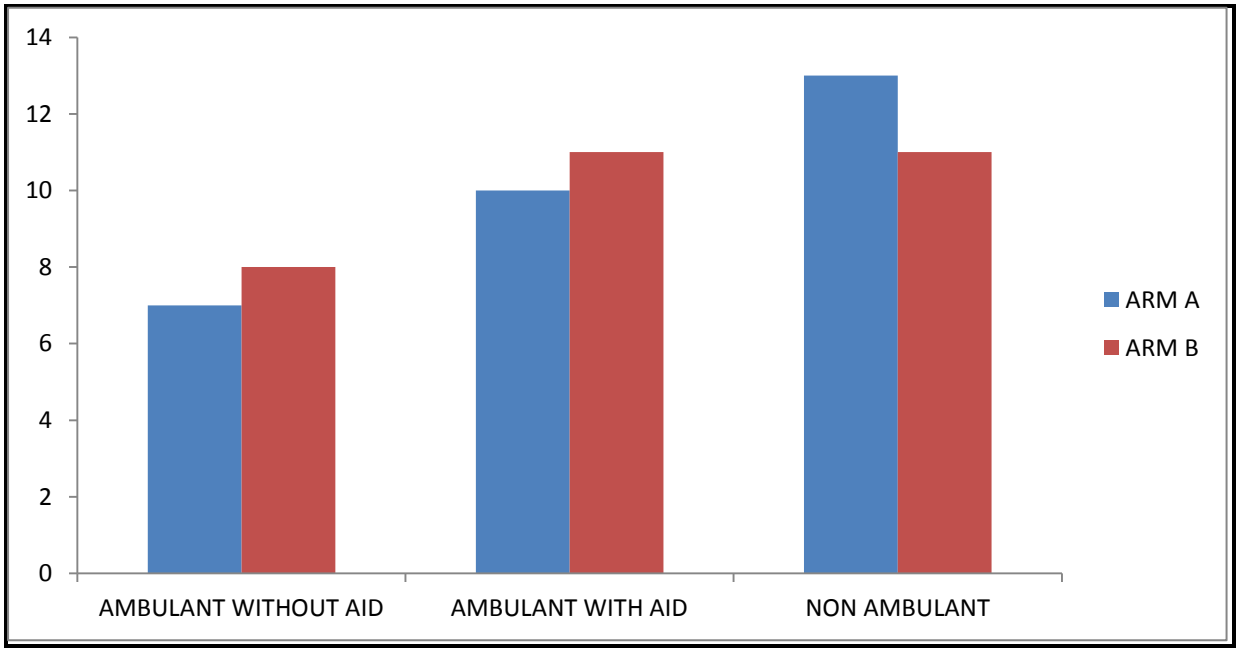

CHART 10- AMBULATORY STATUS BEFORE RADIATION

RESPONSE TO RADIATION AT 1 MONTH

All patients were available for follow-up at one month after radiation. Clinical examination was done to assess overall response to radiation.

Improvement of motor function was defined by improvement of point in scoring system compared to baseline.

Deterioration of motor function defined by reduction of point in scoring system compared to baseline.

No further progression defined by no change in score compared to baseline.

Overall response regarding motor deficits defined as improvement or no further progression at the end of 1 month.

MOTOR FUNCTION AFTER RADIATION	NUMBER	PERCENT
IMPROVEMENT	21/60	35%
NO PROGRESSION	32/60	53.33%
DETERIORATION	07/60	11.66%
OVERALL RESPONSE TO RADIATION	53/60	88.33%

TABLE 23- RESPONSE TO RADIATION IN ENTIRE COHORT

At the end of one month 21 patients had an improvement in motor function.

7 patients deteriorated further.

32 patients did not show improvement but did not deteriorate.

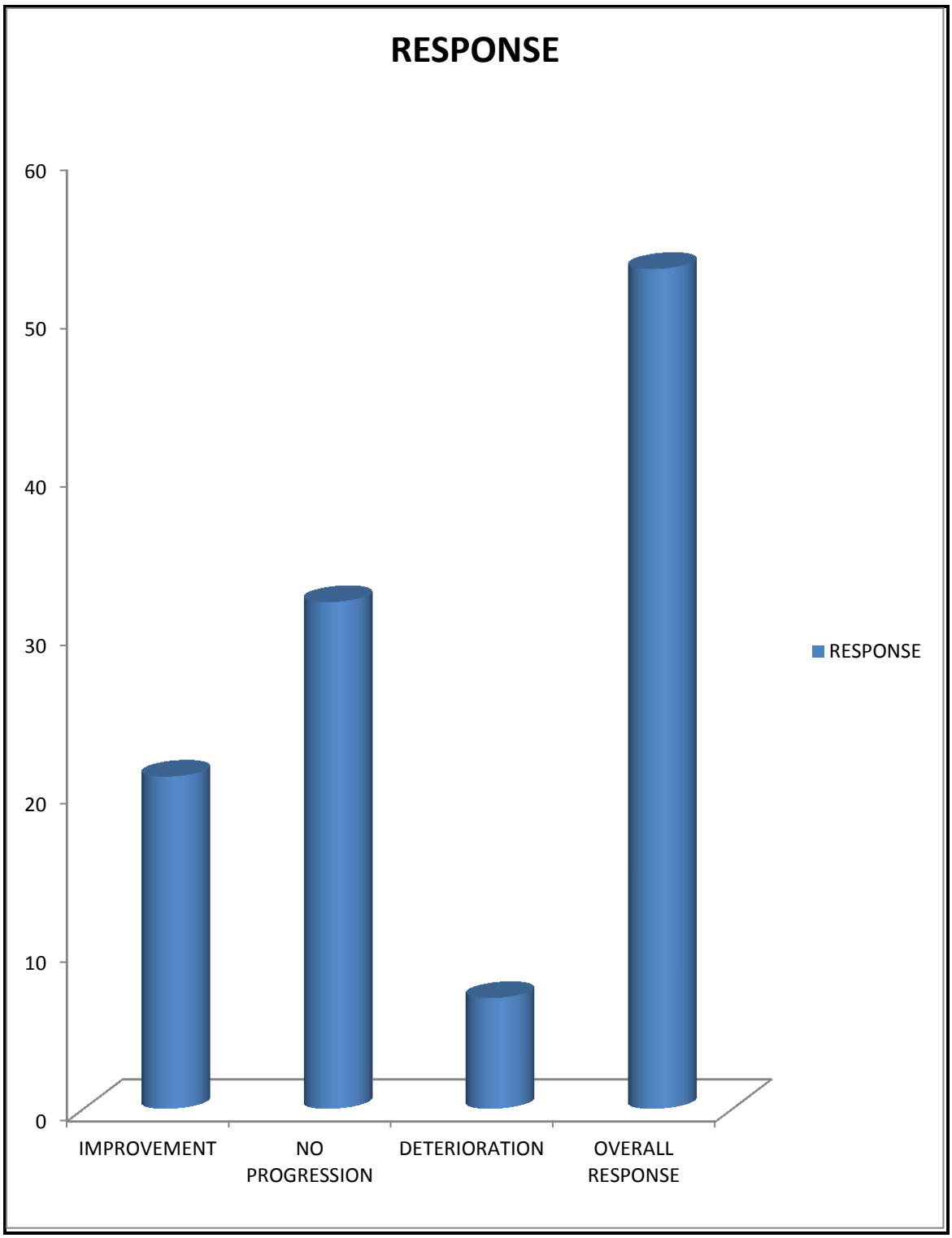

CHART 11- RESPONSE TO RADIATION AT 1 MONTH IN ENTIRE POPULATION

MOTOR FUNCTION AT ONE MONTH	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
IMPROVEMENT	10/30	33.33%	11/30	36.66%	0.9
NO PROGRESSION	16/30	53.33%	16/30	53.33%	
DETERIORATION	04/30	13.33%	03/30	10%	
OVERALL RESPONSE TO RADIATION	26/30	86.66%	27/30	90%	

TABLE 24- RESPONSE TO RADIATION AT 1 MONTH

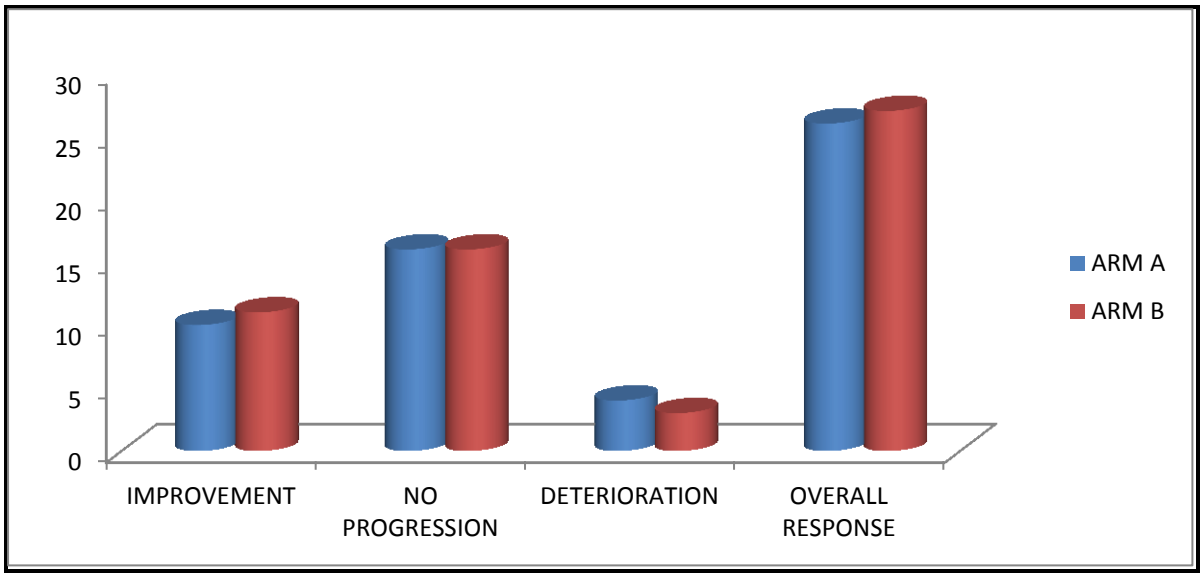

CHART 12- RESPONSE TO RADIATION AT 1 MONTH

33.3% patients in ARM A and 36.66% patients in ARM B had improvement in motor function. 53.33% patients in both arm had no progression in deficit. 13.33% patients in ARM A and 10% in AMR B deteriorated.

p-value by chi-square test was 0.9 which is not significant. Overall response rate at month was not significantly different between the arms.

AMBULATORY RATE AT ONE MONTH AFTER RADIATION

AMBULATORY STATUS AT ONE MONTH	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
AMBULANT	20	66.66%	21	70%	0.78
NOT AMBULANT	10	33.33%	09	30%	
TOTAL	30	100%	30	100%	

TABLE 25- AMBULATORY RATE AT ONE MONTH AFTER RADIATION

66.66% in ARM A and 70% in ARM B were ambulant at one month.

33.33% in ARM A and 30% in ARM B were not ambulant.

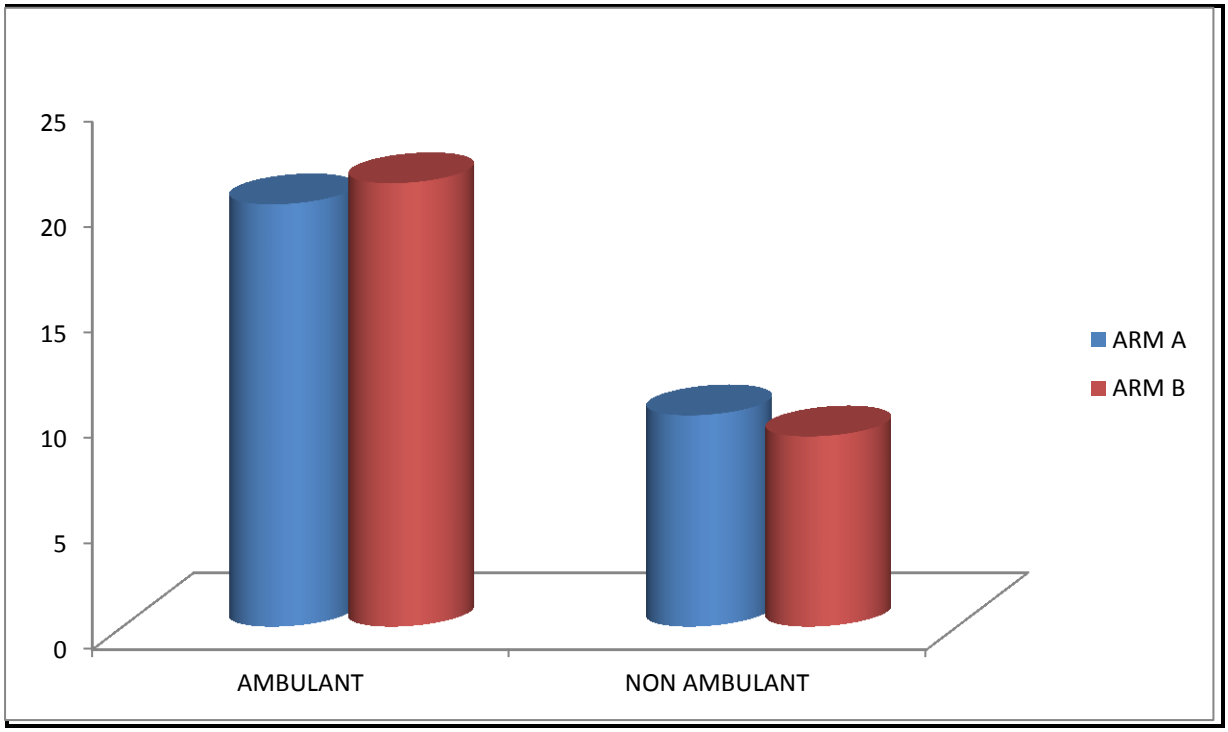

CHART 13- AMBULATORY RATE AT ONE MONTH AFTER RADIATION

AGE DISTRIBUTION AND OVERALL RESPONSE

	ARM A	ARM B	p-value
< 50 YEARS	7/8	8/9	.54
50 – 60 YEARS	12/14	15/16	
> 60 YEARS	7/8	4/5	
TOTAL	26/30	27/30	

TABLE 26- AGE DISTRIBUTION AND RESPONSE

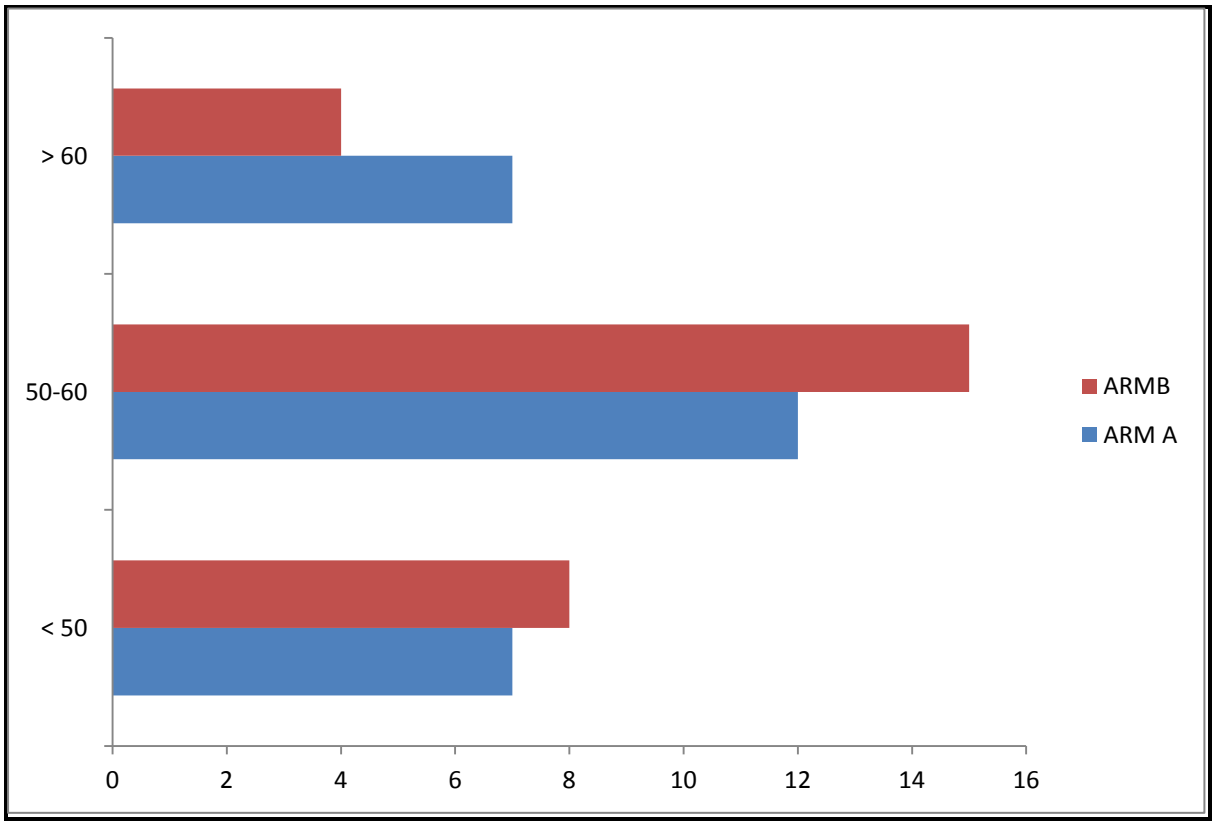

CHART 14- AGE DISTRIBUTION AND RESPONSE

GENDER DISTRIBUTION AND OVERALL RESPONSE

	ARM A	ARM B	p-value
FEMALE	11/13	11/12	.90
MALE	15/17	16/18	
TOTAL	26/30	27/30	

TABLE 27- GENDER DISTRIBUTION AND RESPONSE

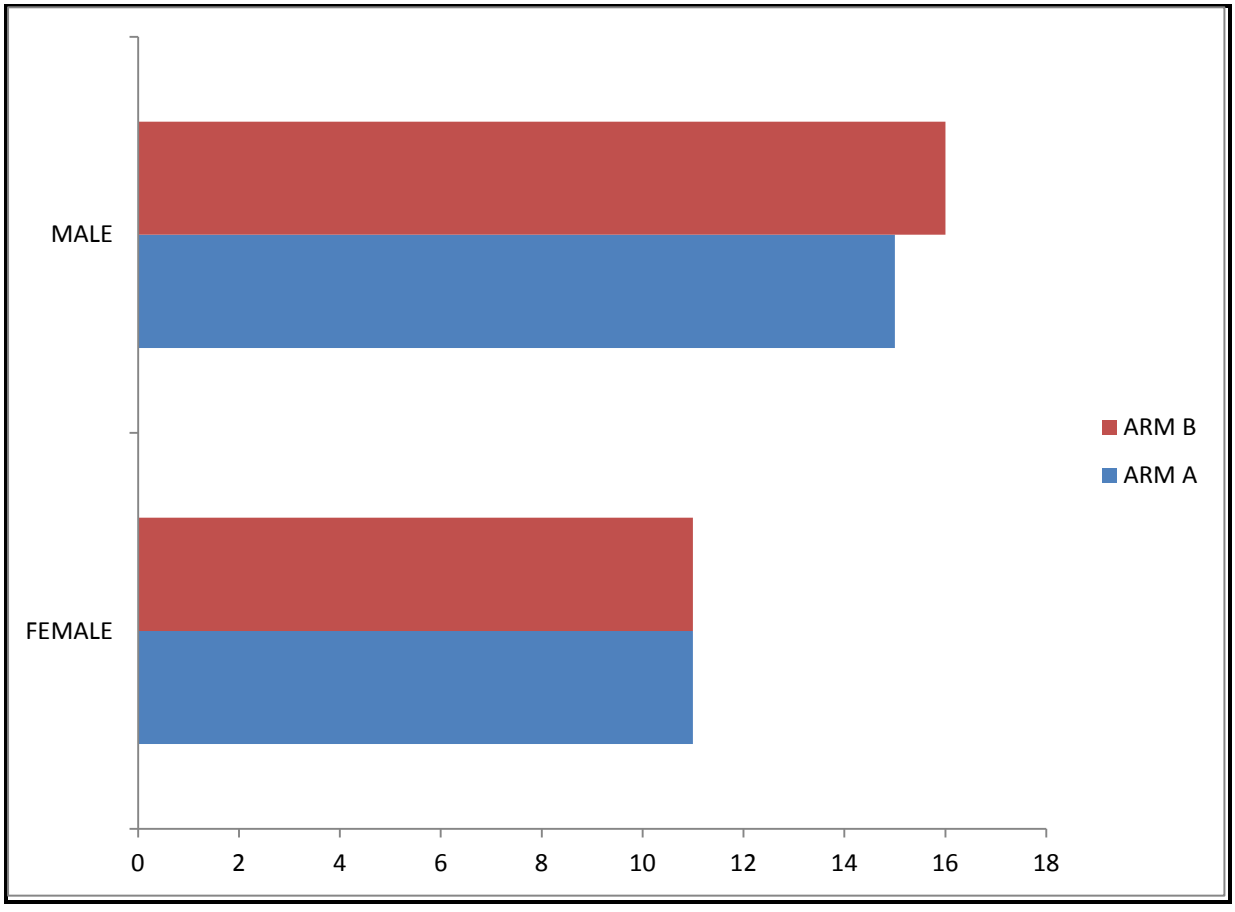

CHART 15- GENDER DISTRIBUTION AND RESPONSE

PERFORMANCE STATUS AND OVERALL RESPONSE

ECOG STATUS	ARM A	ARM B	p-value
1-2	5/5	6/6	.78
3-4	21/25	21/24	
TOTAL	26/30	27/30	

TABLE 28- PERFORMANCE STATUS AND RESPONSE

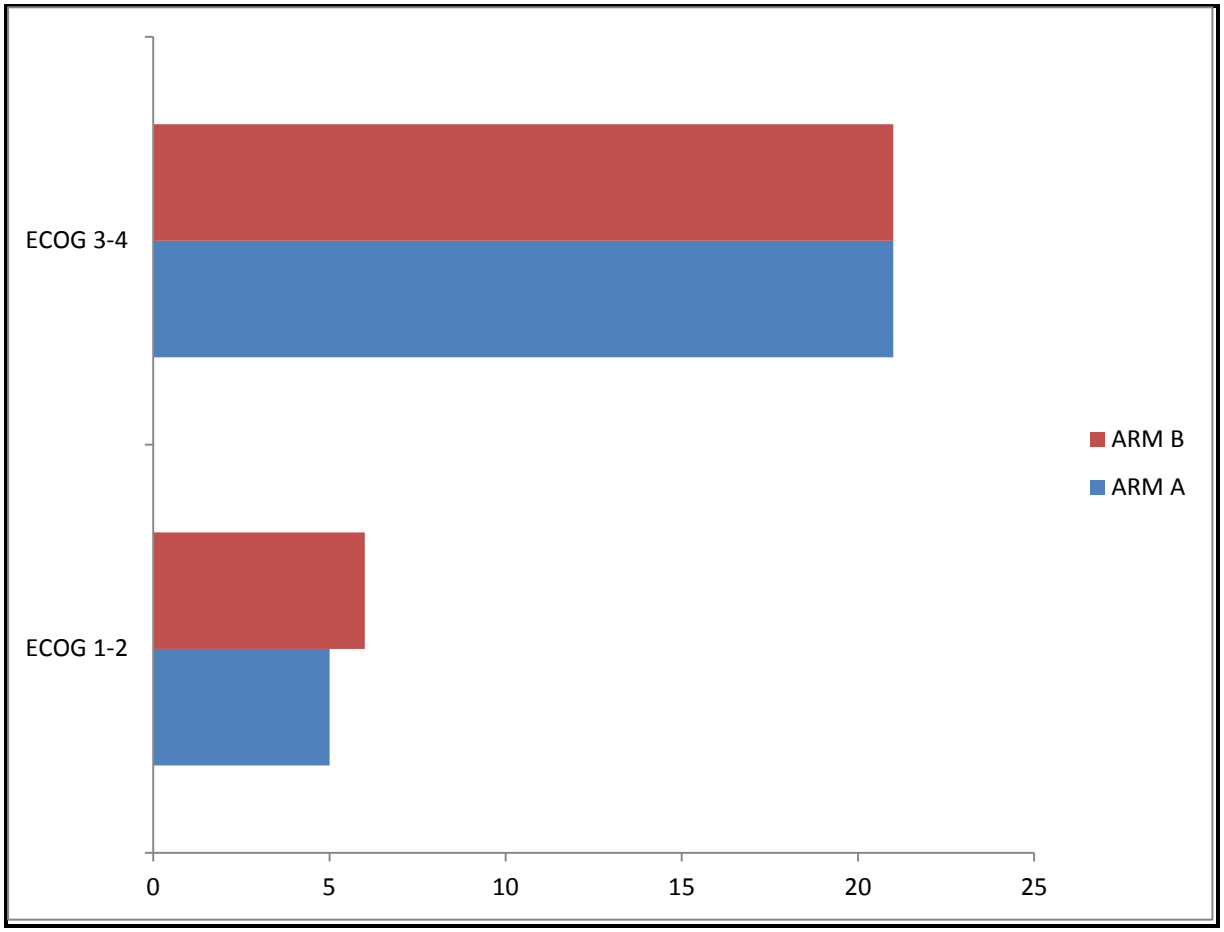

CHART 16- PERFORMANCE STATUS AND RESPONSE

NUMBER OF VERTEBRA INVOLVED AND OVERALL RESPONSE

	ARM A	ARM B	p-value
SINGLE	12/13	11/12	.69
MULTIPLE	14/17	16/18	
TOTAL	26/30	27/30	

TABLE 29- VERTEBRAL INVOLVEMENT AND RESPONSE

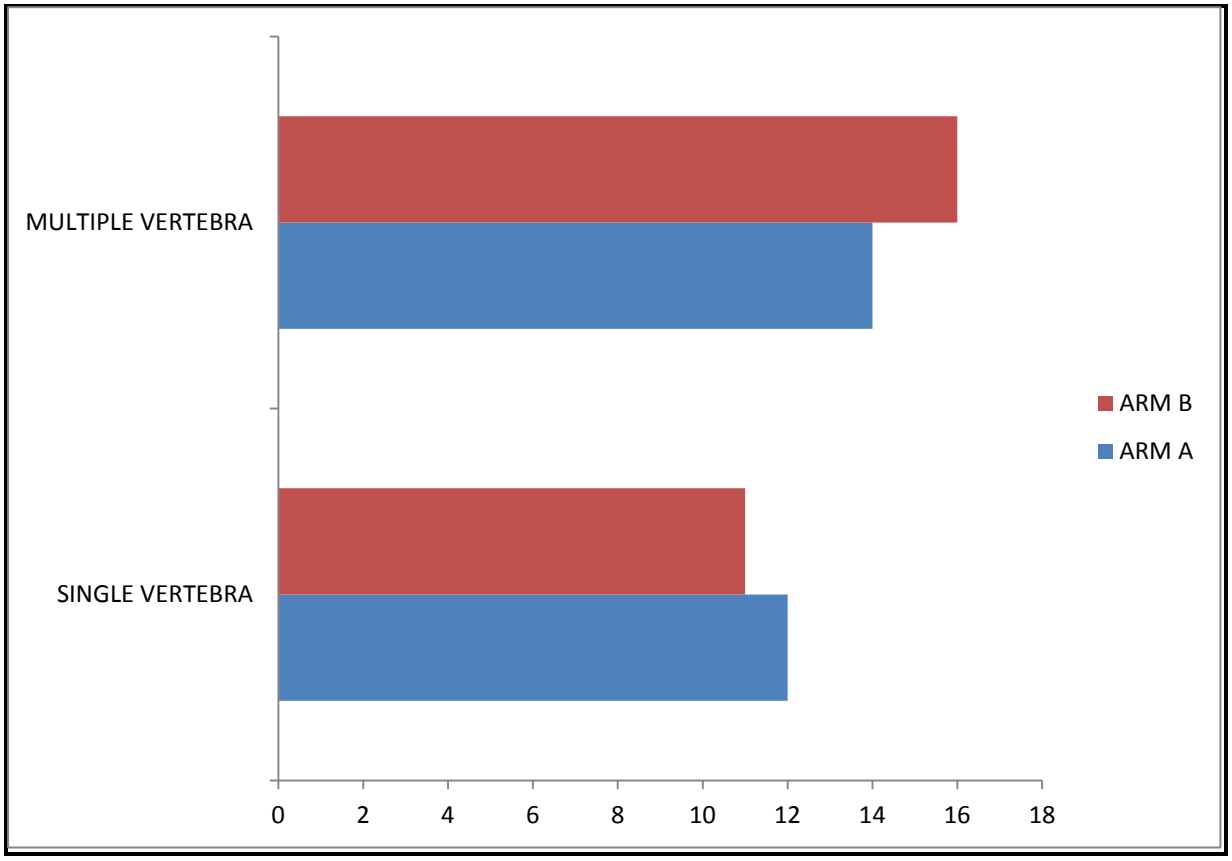

CHART 17- VERTEBRAL INVOLVEMENT AND RESPONSE

ONSET OF MSCC AND OVERALL RESPONSE

	ARM A	ARM B	p-value
< 6 MONTHS	10/12	9/10	.69
> 6 MONTHS	16/18	18/20	
TOTAL	26/30	27/30	

TABLE 30- ONSET OF MSCC AND RESPONSE

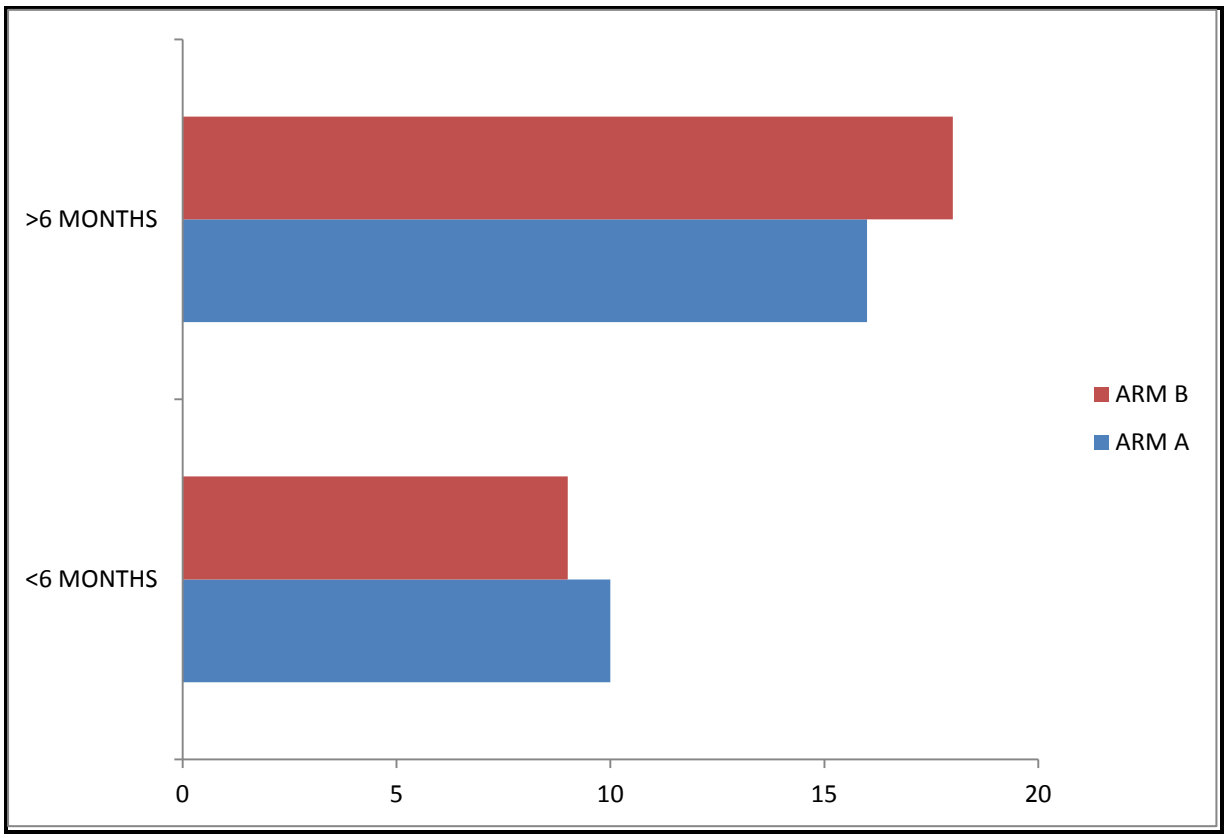

CHART 18- ONSET OF MSCC AND RESPONSE

PRIMARY SITE AND OVERALL RESPONSE

PRIMARY SITE	ARM A	ARM B
LUNG	8/10	6/7
BREAST	6/7	7/8
PROSTATE	5/5	6/6
RECTUM	3/3	¾
EOPHAGUS	2/3	2/2
STOMACH	0	1/1
PANCREAS	1/1	0
RCC	1/1	1/1
THYROID	0	1/1
TOTAL	26/30	27/30

TABLE 31- PRIMARY SITE AND RESPONSE

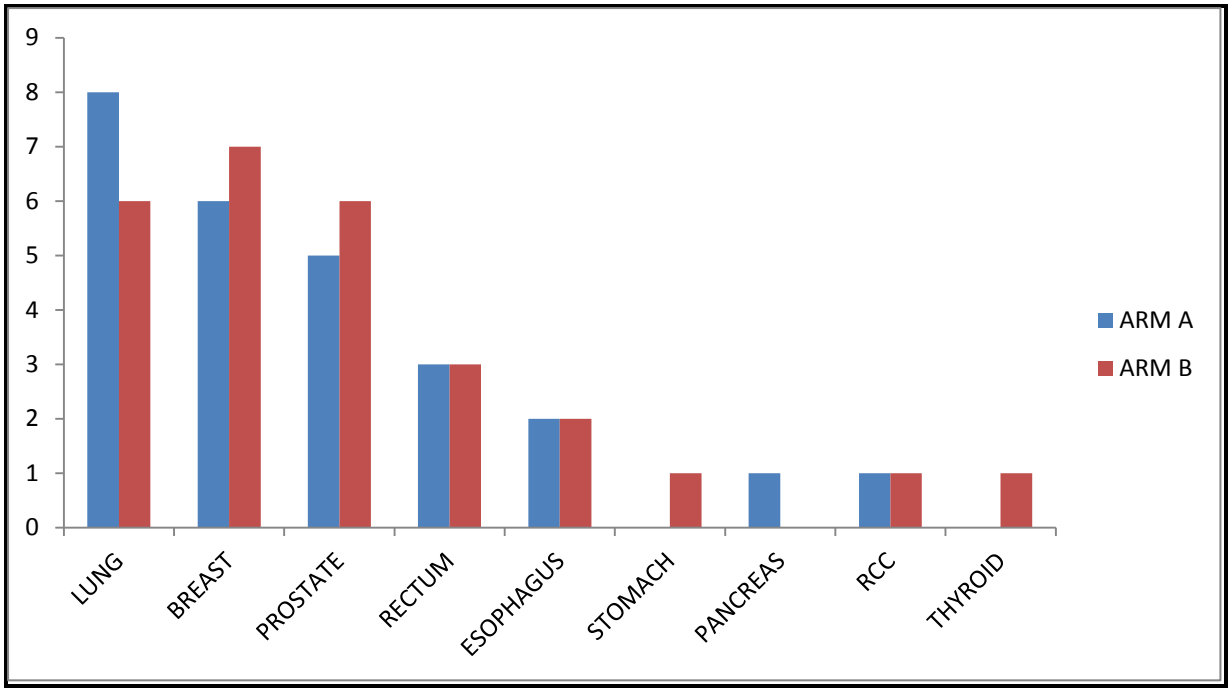

CHART 19- PRIMARY SITE AND RESPONSE

AMBULATORY STATUS BEFORE RADIATION AND OVERALL RESPONSE

	ARM A	ARM B	p-value
AMBULATORY WITHOUT AID	7/7	8/8	.54
AMBULATORY WITH AID	10/10	11/11	
NON AMBULATORY	9/13	8/11	
TOTAL	26/30	27/30	

TABLE 32- AMBULATORY STATUS BEFORE RADIATION OVERALL RESPONSE

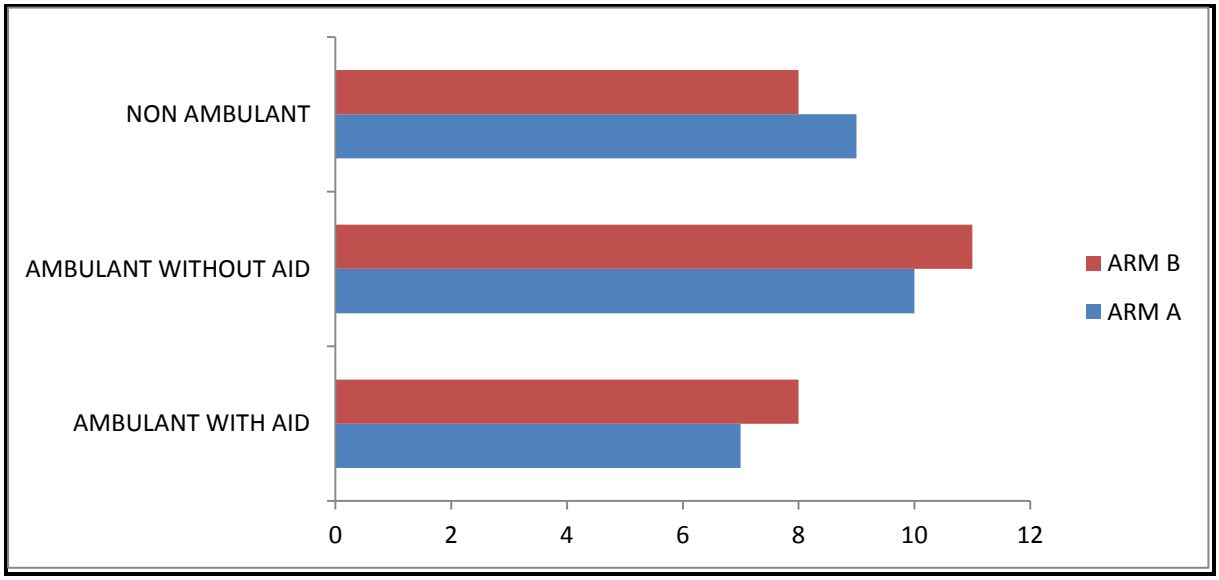

CHART 20- AMBULATORY STATUS BEFORE RADIATION AND RESPONSE

Overall response to radiation was not significantly different between the arms. It was not affected by age, gender, performance status, number of vertebra involved, duration to development of MSCC, primary tumour and ambulatory status. For all these factors the overall response was not significantly different between the arms.

ACUTE TOXICITY

ACUTE TOXICITY	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
GRADE 1	10	33.33%	11	36.66%	.90
GRADE 2	4	13.33%	4	13.33%	
GRADE 3	0	-	0	-	
GRADE 4	0	-	0	-	

TABLE 33- ACUTE TOXICITY

Patients were assessed for acute toxicities of skin, oesophagus, upper gastrointestinal tract and haematological toxicity. None of the patients had grade 3 or 4 toxicities as per RTOG grade. Both treatment arms were tolerated well.

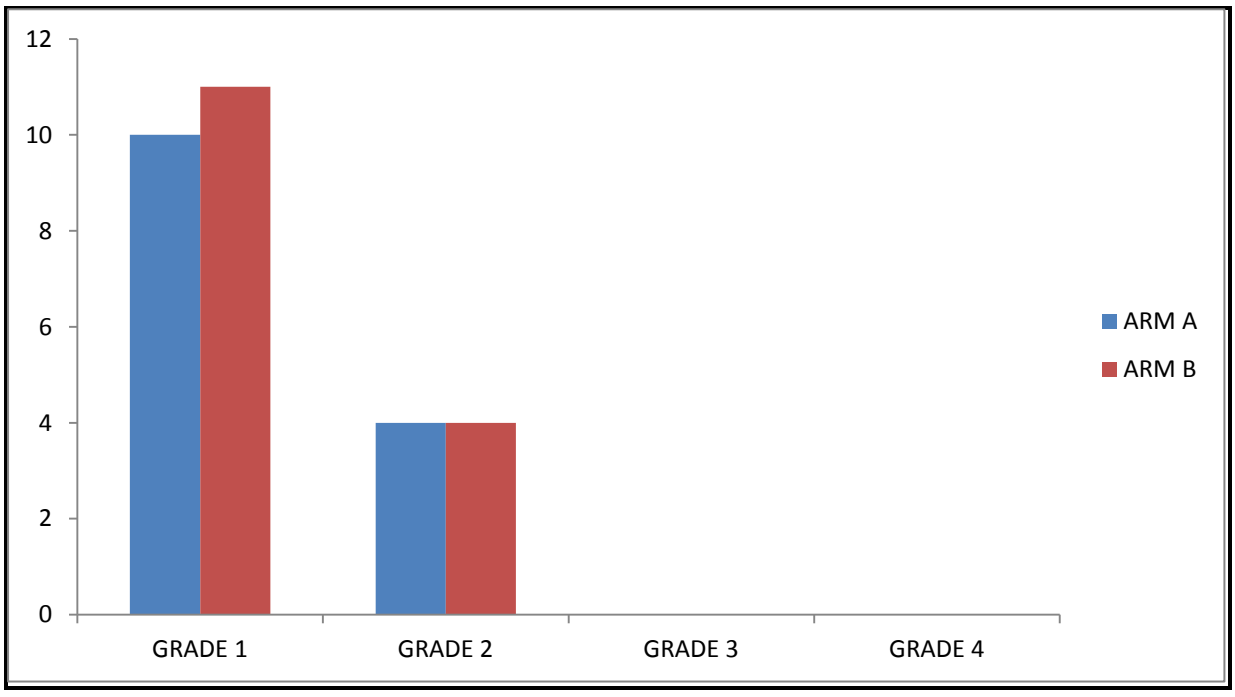

CHART 21- ACUTE TOXICITY

ASSESSMENT AT 6 MONTHS

At six months of follow-up some patients in both arms had died. 24 patients in ARM A were alive after 6 months and were available for follow-up assessment. 25 patients in ARM B were alive.

4 patients in ARM A had deterioration in motor function after radiation and 3 of them had died by 6 months. The remaining 1 patient had paralysis lower limb muscle and was non ambulant. 6 other patients who had response to radiation died by 6 months.

Out of the 24 patients available at follow-up 4 had developed second vertebral metastases within 6 months and were irradiated.

3 patients in ARM A had deterioration in motor function after radiation and one among them had died by 6 months. The remaining 2 patient had paralysis in lower limb muscle and were non ambulant. 4 other patients who had response to radiation died by 6 months.

Out of the 25 patients available at follow-up 3 had developed second vertebral metastases within 6 months and were irradiated.

There was no statistically significant difference between the ambulatory status in the study arms at the end of six months.

AMBULATORY STATUS AT SIX MONTHS	ARM A		ARM B		p-value
	NUMBER	PERCENT	NUMBER	PERCENT	
AMBULANT	12	50%	14	56%	0.67
NOT AMBULANT	12	50%	11	44%	
TOTAL	24	100%	25	100%	

TABLE 34- AMBULATORY STATUS AT 6 MONTHS

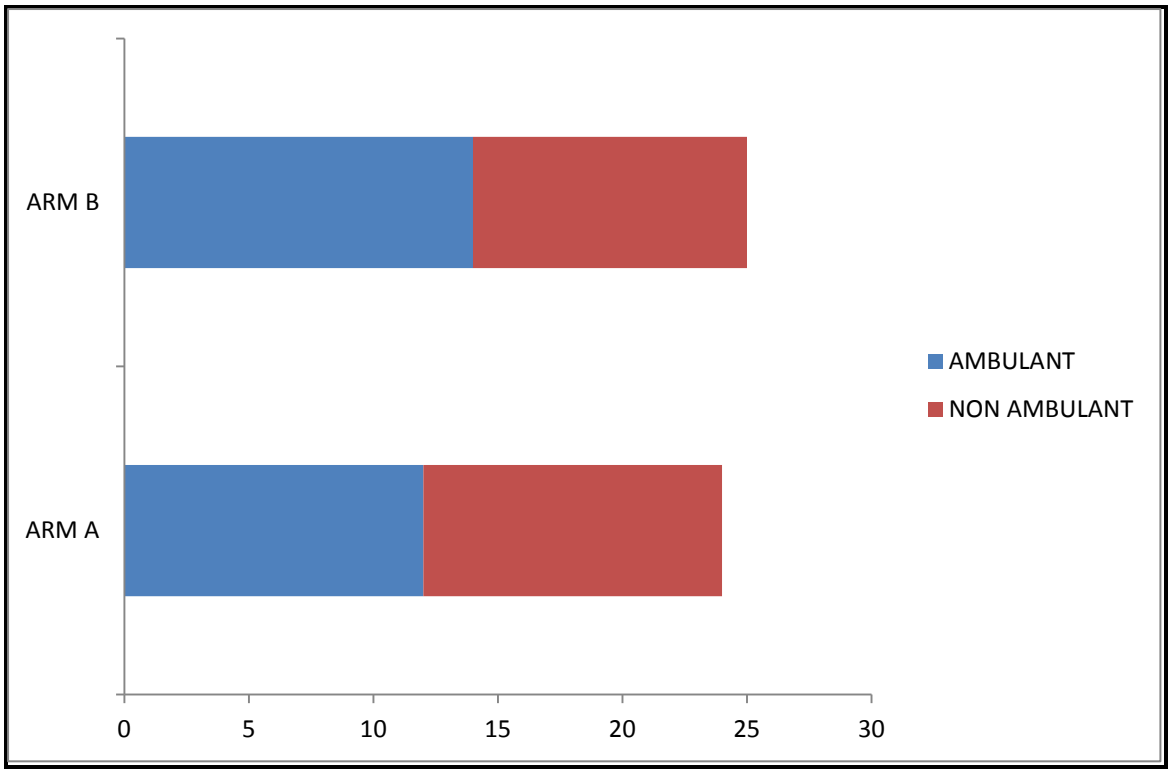

CHART 22- - AMBULATORY STATUS AT 6 MONTHS

Conclusion

CONCLUSION

Results of the study showed that overall response to radiation and ambulatory status of patients post irradiation were similar in both arms. There was no significant difference between the arms.

Age, gender, performance status, number of vertebra involved, time to develop MSCC, ambulatory status did not influence a difference between study arms.

However, recurrence rates between arms was not analysed due to shorter follow-up period. Considering the fact that expected survival of many patients is poor it might not make an impact. For a small proportion of patients who might survive longer recurrence pattern might influence radiation fractionation.

In general patients with MSCC have a poor survival and short course fractionation with 4 Gy x 5 fractions can be considered instead of the standard 3 Gy x 10 fractions.

Discussion

DISCUSSION

Individually tailored radiation approach is necessary in metastatic cord compression. Expected life span and socio economic status of the patient play a significant role in decision making.

Several radiation fractionations have been employed. Shorter courses from one day to one week and longer ones from two to four weeks can be used.

Retrospective and prospective data have shown that motor function and ambulatory status do not vary significantly between various regimens. Results of the present study also showed no significant difference in motor function and ambulatory status.

In-field recurrence should be considered in choosing fractionation regimen in patients expected to have a longer survival. Non randomised retrospective data have shown that shorter courses are associated with more recurrences beyond two years.

Future research is needed to find patient population who could benefit from a shorter fractionation of single 8 Gy alone. Development of tools to predict the longer survival and recurrence patterns can help in deciding radiation fractionation.

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INFORMATION TO PARTICIPANTS

Title: **"COMPARING RADIOTHERAPY WITH 4 GY x 5 FRACTIONS VS 3 GY x 10 FRACTIONS FOR METASTATIC SPINAL CORD COMPRESSION "**

Name of Participant:
Name of the Principal(co – investigator) :DR.P R.HARISH KUMAR
Name of the institution : Department of radiotherapy, RGGGH, MMC.

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Metastatic spinal cord compression is on of the most devastating neurological complication affecting 5%-10% of cancer patients resulting from spine metastases extending into the epidural space.Pain is the most common initial clinical symptom. Neurological dysfunction ensues within weeks and is irreversible if not treated promptly.MSCC is an oncologic emergency requiring immediate treatment.Functional outcome could be improved with decompressive surgery plus stabilization of involved vertebrae followed by RT. Because of narrow inclusion criteria, the addition of surgery seems suitable for only 10% to 15% of patients. Therefore, RT alone is the standard treatment for most patients with MESCC, particularly for those with poor or intermediate survival prognoses.

˙We want to compare the effectiveness of two different fractionation schedules routinely used to treat patients with metastatic spinal cord compression .We have obtained permission from the Institutional Ethics Committee.

The study design

Double arm prospective study

Study Procedures

The study involves patients with metastatic spinal cord compression causing lowerlimb motor dysfunction with a biopsy proven primary malignancy of any site. Baseline motor function score is evaluated. Radiotherapy is planned and executed as per the allotted arm after verifying the fields with Xray simulation. Every month when you come for the routine follow up, the study physician will examine you and evaluate the motor function score .Some [blood /clinical examination other] tests will be carried out at each visit. [… … ml of blood will be collected at each visit. Blood collection involves prick with a needle and syringe.] These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you .In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.
You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator | Signature of Participant

Date | Date

INFORMED CONSENT FORM

TITLE OF THE STUDY **"COMPARING RADIOTHERAPY WITH 4 GY x 5 FRACTIONS VS 3 GY x 10 FRACTIONS FOR METASTATIC SPINAL CORD COMPRESSION "**

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator) : **DR.P R.HARISH KUMAR**

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising myfree power of choice, hereby give my consent to be included as a participant in **"COMPARING RADIOTHERAPY WITH 4 GY x 5 FRACTIONS VS 3 GY x 10 FRACTIONS FOR METASTATIC SPINAL CORD COMPRESSION "**

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *****
8. I have not participated in any research study within the past 12month(s). *****
9. I agree to under go complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)
Name _____ Signature_____ Date_____
Name and Signature of impartial witness (required for illiterate patients):
Name _____ Signature_____ Date_____
Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent
Name _____ Signature_____ Date_____

ஆராய்ச்சி ஒப்புதல் படிவம்

முதுகெலும்பிற்கு பரவியுள்ள புற்றுநோய்க்கு கொடுக்கப்படும் இருவேறு கதிர்வீச்சு சிகிச்சை முறைகளின் பலன்களையும், பின்விளைவுகளையும் பற்றி ஆராய்தல்

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
எண்	:	ஆராய்ச்சி சேர்க்கை எண்	:
பால்	:		

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்குத் தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

எனக்கு புற்றுநோய் இருக்கும் பகுதியில் கதிர்வீச்சு சிகிச்சை செய்துகொள்ள சம்மதம்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் முதுகெலும்பிற்கு பரவியுள்ள புற்றுநோய்க்கு கொடுக்கப்படும் இருவேறு கதிர்வீச்சு சிகிச்சை முறைகளின் விவரங்கள் கொண்ட தகவல்தாளைப் பெற்றுக்கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை மற்றும் புற்றுநோய் மருந்துகள் பெற்றுக்கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும் சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்துகொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம் தெரிவிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

தேதி

ஆராய்ச்சி தகவல்தாள்

ஆராய்ச்சியாளர் பெயர் :

முதுகெலும்பிற்கு பரவியுள்ள புற்றுநோய்க்கு கொடுக்கப்படும் இருவேறு கதிர்வீச்சு சிகிச்சை முறைகளின் பலன்களையும், பின்விளைவுகளையும் பற்றி ஆராய்தல்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் புற்று நோயாளிகளிடம் கதிர்வீச்சு சிகிச்சை பற்றிய ஆராயச்சி.

முதுகெலும்பிற்கு பரவியுள்ள புற்றுநோய்க்கு கொடுக்கப்படும் இருவேறு கதிர்வீச்சு சிகிச்சை முறைகளின் பலன்களையும், பின்விளைவுகளையும் பற்றி ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய திசுக்களை எடுத்து சில பரிசோதனைக்கு உட்படுத்து அதன் தகவல்களை ஆராய்வோம். இதனால் உங்களுடைய சிகிச்சைக்கு பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறேம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

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ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.P.R.Harish Kumar
Post Graduate in M.D. Radiotherapy
Department of Radiation Oncology
Madras Medical College
Chennai 600 003

Dear Dr.P.R.Harish Kumar,

The Institutional Ethics Committee has considered your request and approved your study titled **"COMPARING RADIOTHERAPY WITH 4 GY x 5 FRACTIONS VS 3 GY x 10 FRACTIONS FOR METASTATIC SPINAL CORD COMPRESSION " - NO.07062017**

The following members of Ethics Committee were present in the meeting hold on **06.06.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5.Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6.Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
7.Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
8.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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CERTIFICATE

This is to certify that the dissertation entitled **“COMPARING RADIOTHERAPY WITH 4GY x 5 FRACTIONS VS 3GY x 10 FRACTIONS FOR METASTATIC SPINAL CORD COMPRESSION”** of the candidate Dr.HARISH KUMAR.PR, with Registration Number **201619003** for the award of **M.D. Degree** in the Branch of **Radiotherapy**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from Introduction to Conclusion pages and result shows **___ Percentage** of Plagiarism in the Dissertation.

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